Clinical trial results:
A Randomized, Double-Blind, Placebo Controlled Trial to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Paediatric (10 - 17 Years Old) and Adult Patients With Type 2 Diabetes

Summary

EudraCT number	2011-004584-67
Trial protocol	DE GB Outside EU/EEA
Global end of trial date	04 March 2014

Results information

Result version number	v2 (current)
This version publication date	07 July 2016
First version publication date	20 March 2015
Version creation reason	• Correction of full data set Typo corrections

Trial information

Trial identification

Sponsor protocol code	PKD11475

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01572649
WHO universal trial number (UTN)	U1111-1124-3136

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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000916-PIP01-10
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	14 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to investigate the effects of a single subcutaneous lixisenatide dose of 5 microgram (mcg) and 10 mcg as compared to placebo in reducing postprandial plasma glucose (PPG) assessed as area under the plasma glucose concentration curve after a standardized liquid meal (breakfast) in type 2 diabetic paediatric population (10 to 17 years old) and adults as controls.

Protection of trial subjects:

Paediatric Subjects:
The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anaesthesia may have been used to minimize distress and discomfort.

Adult 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	14 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	United Kingdom: 4
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	South Africa: 4
Worldwide total number of subjects	24
EEA total number of subjects	4

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)	2
Adolescents (12-17 years)	10
Adults (18-64 years)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 centres in 4 countries between 14 May 2012 and 04 March 2014.

Pre-assignment

Screening details:

A total of 78 subjects (25 paediatrics and 53 adults) were screened and 24 (12 in each paediatric and adult) 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	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Paediatric

Arm description:

Paediatric subjects (10 years to less than [<] 18 years of age) received single dose of lixisenatide 5 microgram (mcg), 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as subcutaneous (SC) injection on Day 1 of either of the 3 treatment periods in a crossover design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.

Arm type	Experimental-Placebo Cross-over
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 5 microgram (mcg) or 10 mcg using the pen-type injector (OptiClik ®), 30 minutes prior to a standardized liquid breakfast meal.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to lixisenatide using the pen-type injector (OptiClik ®), 30 minutes prior to a standardized liquid breakfast meal.

Arm title	Adult

Arm description:

Adult subjects (18 years to 65 years of age) received single dose of lixisenatide 5 mcg, 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as SC injection on Day 1 of either of the 3 treatment periods in a cross-over design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.

Arm type	Experimental-Placebo Cross-over

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 5 mcg or 10 mcg using the pen-type injector (OptiClik ®), 30 minutes prior to a standardized liquid breakfast meal.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to lixisenatide using the pen-type injector (OptiClik ®), 30 minutes prior to a standardized liquid breakfast meal.

Number of subjects in period 1	Paediatric	Adult
Started	12	12
Completed	12	12

Baseline characteristics

Reporting groups	
Reporting group title	Paediatric
Reporting group description:	
Paediatric subjects (10 years to less than [<] 18 years of age) received single dose of lixisenatide 5 microgram (mcg), 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as subcutaneous (SC) injection on Day 1 of either of the 3 treatment periods in a crossover design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.	
Reporting group title	Adult
Reporting group description:	
Adult subjects (18 years to 65 years of age) received single dose of lixisenatide 5 mcg, 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as SC injection on Day 1 of either of the 3 treatment periods in a cross-over design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.	

Reporting group values	Paediatric	Adult	Total
Number of subjects	12	12	24
Age categorical Units: Subjects			
Children (2-11 years)	2	0	2
Adolescents (12-17 years)	10	0	10
Adults (18-64 years)	0	12	12
Age continuous Units: years			
arithmetic mean	13.9	51.3	
standard deviation	± 2.2	± 5.9	-
Gender categorical Units: Subjects			
Female	6	3	9
Male	6	9	15
Race Units: Subjects			
Caucasian/White	1	6	7
Asian/Oriental	0	1	1
Other	11	5	16
Weight Units: kilogram (kg)			
arithmetic mean	84.69	92.58	
standard deviation	± 23.31	± 17.8	-
Body Mass Index (BMI) Units: kilogram per square meter (kg/m^2)			
arithmetic mean	31.42	31.79	
standard deviation	± 6.51	± 3.05	-
Glycated hemoglobin (HbA1c) Units: percentage of haemoglobin			
arithmetic mean	8.65	8.43	
standard deviation	± 1.14	± 0.69	-

End points

End points reporting groups

Reporting group title	Paediatric

Reporting group description:

Paediatric subjects (10 years to less than [<] 18 years of age) received single dose of lixisenatide 5 microgram (mcg), 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as subcutaneous (SC) injection on Day 1 of either of the 3 treatment periods in a crossover design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.

Reporting group title	Adult

Reporting group description:

Adult subjects (18 years to 65 years of age) received single dose of lixisenatide 5 mcg, 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as SC injection on Day 1 of either of the 3 treatment periods in a cross-over design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.

Subject analysis set title	Placebo: Paediatric
Subject analysis set type	Per protocol

Subject analysis set description:

Paediatric subjects (10 years to <18 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mcL) or lixisenatide 10 mcg (100 mcL) by SC route.

Subject analysis set title	Lixisenatide 5 mcg: Paediatric
Subject analysis set type	Per protocol

Subject analysis set description:

Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 5 mcg (50 mcL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level).

Subject analysis set title	Lixisenatide 10 mcg: Paediatric
Subject analysis set type	Per protocol

Subject analysis set description:

Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 10 mcg (100 mcL) by SC route.

Subject analysis set title	Placebo: Adult
Subject analysis set type	Per protocol

Subject analysis set description:

Adult subjects (18 years to 65 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mcL) or lixisenatide 10 mcg (100 mcL) by SC route.

Subject analysis set title	Lixisenatide 5 mcg: Adult
Subject analysis set type	Per protocol

Subject analysis set description:

Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 5 mcg (50 mcL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level).

Subject analysis set title	Lixisenatide 10 mcg: Adult
Subject analysis set type	Per protocol

Subject analysis set description:

Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 10 mcg (100 mcL) by SC route.

Primary: Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve From Time 0.5 Hours to 4.5 Hours

End point title	Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve 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 3-1000 milligram per deciliter (mg/dL), with 1 mg/dL as limit of detection (LOD). Measurement was done using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal plasma glucose concentration (time: 0.5 hours). Evaluable pharmacodynamic (PD)

population included all randomized and treated subjects without any critical/major deviation related to IMP administration, for whom at least 1 PD parameter was considered sufficient and interpretable.

End point type	Primary

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Placebo: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	12
Units: millimole*hour per litre (mmol*h/L)				
least squares mean (standard error)	9.63 (± 3.95)	5.72 (± 3.99)	8.11 (± 4.08)	16.6 (± 2.46)

End point values	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: millimole*hour per litre (mmol*h/L)				
least squares mean (standard error)	8.03 (± 2.95)	1.11 (± 2.85)		

Statistical analyses

Statistical analysis title	Lixisenatide 5 mcg vs Placebo: Paediatric

Statistical analysis description:

The linear fixed effects model used includes treatment, sequence and period as fixed effects, and subject-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 5 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 9 instead of 18.

Comparison groups	Lixisenatide 5 mcg: Paediatric v Placebo: Paediatric
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0681
Method	Linear fixed effects model
Parameter estimate	Least squares mean difference
Point estimate	-3.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.17
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	1.97

Statistical analysis title	Lixisenatide 10 mcg vs Placebo: Paediatric

Statistical analysis description:

The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 10 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 9 instead of 18.

Comparison groups	Placebo: Paediatric v Lixisenatide 10 mcg: Paediatric
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4359
Method	Linear fixed effects model
Parameter estimate	Least squares mean difference
Point estimate	-1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.59
upper limit	2.56
Variability estimate	Standard error of the mean
Dispersion value	1.89

Statistical analysis title	Lixisenatide 5 mcg vs Placebo: Adult

Statistical analysis description:

The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 5 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 12 instead of 24.

Comparison groups	Placebo: Adult v Lixisenatide 5 mcg: Adult
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0104
Method	Linear fixed effects model
Parameter estimate	Least squares mean difference
Point estimate	-8.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.91
upper limit	-2.23
Variability estimate	Standard error of the mean
Dispersion value	3.05

Statistical analysis title	Lixisenatide 10 mcg vs Placebo: Adult

Statistical analysis description:

The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 10 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 12 instead of 24.

Comparison groups	Placebo: Adult v Lixisenatide 10 mcg: Adult
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Linear fixed effects model
Parameter estimate	Least squares mean difference
Point estimate	-15.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.59
upper limit	-9.38
Variability estimate	Standard error of the mean
Dispersion value	2.93

Secondary: Plasma Glucose Area Under The Plasma Concentration-Time Curve From Time 0.5 Hours to 4.5 Hours

End point title	Plasma Glucose Area Under The Plasma Concentration-Time Curve 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 3-1000 mg/dL, with 1 mg/dL LOD. The area under the plasma glucose concentration time curve (AUC0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours). Analysis was performed in evaluable PD population.

End point type	Secondary

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Placebo: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	12
Units: mmol*h/L				
least squares mean (standard error)	44.5 (± 3.91)	40.53 (± 3.94)	42.94 (± 4.03)	54.32 (± 2.46)

End point values	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: mmol*h/L				
least squares mean (standard error)	45.75 (± 2.95)	38.83 (± 2.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial Plasma Glucose (PPG) Excursion

End point title	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 3-1000 mg/dL, with 1 mg/dL LOD. The PPG excursion was calculated as the maximum PPG level determined from time of standardized breakfast (time: 0.5 hours) until 4 hours after breakfast start (time: 4.5 hours) minus the premeal plasma glucose level (time: 0.5 hours). Analysis was performed in evaluable PD population.

End point type	Secondary

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Placebo: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	12
Units: mmol/L				
least squares mean (standard error)	4.58 (± 1.22)	3.08 (± 1.23)	3.46 (± 1.27)	6.58 (± 0.64)

End point values	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: mmol/L				
least squares mean (standard error)	3.81 (± 0.75)	2.26 (± 0.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Glucagon AUC(0:30-4:30h)

End point title	Plasma Glucagon AUC(0:30-4:30h)

End point description:

Plasma glucagon was assessed using the radioimmunoassay. The range of the method was 4.7-150 picomol per liter (pmol/L). Plasma Glucagon AUC(0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal plasma glucagon concentration (time: 0.5 hours). Analysis was performed in evaluable PD population.

End point type	Secondary

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Placebo: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	8	9	12
Units: nanogram*hour per litre (ng*h/L)				
least squares mean (standard error)	664.83 (± 19.92)	652.63 (± 22.22)	621.48 (± 20.77)	628.98 (± 26.47)

End point values	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: nanogram*hour per litre (ng*h/L)				
least squares mean (standard error)	612.44 (± 27.9)	575.3 (± 27.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Insulin AUC(0:30-4:30h)

End point title	Serum Insulin AUC(0:30-4:30h)

End point description:

Serum insulin was assessed using Electro Chemiluminescence Immuno Assay (ECLIA). The range of the method was 1-875 milli-international units per litre (mIU/L), with 0.3 mIU/L as LOD. Serum Insulin AUC(0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal serum insulin concentration (time: 0.5 hours). Analysis was performed in evaluable PD population.

End point type	Secondary

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Placebo: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	8	8	12
Units: picomole*hour per litre (pmol*h/L)				
least squares mean (standard error)	1843.81 (± 297.88)	1973.88 (± 243.52)	1602.8 (± 239.93)	1276.36 (± 85.63)

End point values	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	12		
Units: picomole*hour per litre (pmol*h/L)				
least squares mean (standard error)	1181.62 (± 103.75)	802.65 (± 104.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum C-Peptide AUC(0:30-4:30h)

End point title	Serum C-Peptide AUC(0:30-4:30h)

End point description:

Serum C-peptide was assessed using ECLIA. The range of the method was 0.2-25 nanogram per millilitre (ng/mL) with 0.07 ng/mL as LOD. Serum C-Peptide AUC(0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal serum C-peptide concentration (time: 0.5 hours). Analysis was performed in evaluable PD population.

End point type	Secondary

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Placebo: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	8	12
Units: nanomole*hour per litre (nmol*h/L)				
least squares mean (standard error)	9.92 (± 0.56)	9.87 (± 0.59)	9.21 (± 0.58)	8.9 (± 0.48)

End point values	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	12		
Units: nanomole*hour per litre (nmol*h/L)				
least squares mean (standard error)	8.42 (± 0.56)	6.81 (± 0.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Lixisenatide

End point title	Maximum Plasma Concentration (Cmax) of Lixisenatide

End point description:

Lixisenatide plasma concentrations were determined using a validated double-antibody sandwich enzyme-linked immunosorbent assay method with an LLOQ of 5.5 pg/mL. Analysis was performed in evaluable PK population.

End point type	Secondary

End point timeframe:

Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	10	10
Units: picogram per millilitre (pg/mL)				
arithmetic mean (standard deviation)	29.7 (± 14.2)	34.3 (± 25.4)	26 (± 15.4)	56.9 (± 21.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (tmax) of Lixisenatide

End point title	Time to Reach Cmax (tmax) of Lixisenatide

End point description:

Analysis was performed in evaluable PK population.

End point type	Secondary

End point timeframe:

Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	10	10
Units: hour (h)				
median (full range (min-max))	1.25 (0.48 to 3.5)	0.49 (0.48 to 3.55)	1.5 (0.42 to 3.5)	2.5 (0.42 to 3.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve from Time Zero to the Real Time Corresponding to the Last Quantifiable Concentration (AUClast) of Lixisenatide

End point title	Area Under the Concentration Time Curve from Time Zero to the Real Time Corresponding to the Last Quantifiable Concentration (AUClast) of Lixisenatide

End point description:

Area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to the real time corresponding to the last concentration above the limit of quantification. LLOQ = 5.5 pg/mL. Analysis was performed in evaluable PK population.

End point type	Secondary

End point timeframe:

Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	10	10
Units: picogram*hour per millilitre (pg*h/mL)				
arithmetic mean (standard deviation)	99.4 (± 77.7)	108 (± 109)	101 (± 58)	242 (± 90)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration Time Curve Extrapolated to Infinity (AUC) of Lixisenatide

End point title	Area Under The Concentration Time Curve Extrapolated to Infinity (AUC) of Lixisenatide

End point description:

AUC is the area under the serum concentration-time curve from time zero extrapolated to infinite time. Analysis was performed in evaluable PK population.

End point type	Secondary

End point timeframe:

Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2,

End point values	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[1]	0[2]	0[3]	0[4]
Units: pg*hour/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[1] - Analysis was not performed due to insufficient data.

[2] - Analysis was not performed due to insufficient data.

[3] - Analysis was not performed due to insufficient data.

[4] - Analysis was not performed due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: Lixisenatide AUC(0:30-4:30h)

End point title	Lixisenatide AUC(0:30-4:30h)

End point description:

Lixisenatide plasma concentrations were determined using a validated double-antibody sandwich enzyme-linked immunosorbent assay method with an LLOQ of 5.5 pg/mL. The area under the concentration time curve (AUC0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours). Analysis was performed in evaluable PK population.

End point type	Secondary

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

End point values	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	7	10	10
Units: pg*h/mL				
arithmetic mean (standard deviation)	82.5 (± 54.6)	88 (± 76)	77.2 (± 42.4)	181 (± 71.9)

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 2-7 after treatment period 3) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (the time from study drug injection up to 1 day after study drug injection [included] in each treatment period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo: Paediatric

Reporting group description:

Paediatric subjects (10 years to <18 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mcL) or lixisenatide 10 mcg (100 mcL) by SC route.

Reporting group title	Lixisenatide 5 mcg: Paediatric

Reporting group description:

Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 5 mcg (50 mcL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level).

Reporting group title	Lixisenatide 10 mcg: Paediatric

Reporting group description:

Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 10 mcg (100 mcL) by SC route.

Reporting group title	Placebo: Adult

Reporting group description:

Adult subjects (18 years to 65 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mcL) or lixisenatide 10 mcg (100 mcL) by SC route.

Reporting group title	Lixisenatide 5 mcg: Adult

Reporting group description:

Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 5 mcg (50 mcL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level).

Reporting group title	Lixisenatide 10 mcg: Adult

Reporting group description:

Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 10 mcg (100 mcL) by SC route.

Serious adverse events	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Placebo: Adult	Lixisenatide 5 mcg:	Lixisenatide 10 mcg:

		Adult	Adult
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo: Paediatric	Lixisenatide 5 mcg: Paediatric	Lixisenatide 10 mcg: Paediatric
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	2 / 12 (16.67%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo: Adult	Lixisenatide 5 mcg: Adult	Lixisenatide 10 mcg: Adult
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2012	In the context of this single dose study in paediatric and adult patients with Type 2 diabetes mellitus (T2DM) , information given in the clinical protocol about the measurement of plasma glucose in case of eventual hypoglycaemia was clarified. A new secondary endpoint, defined as the area under the plasma glucose concentration-time profile from time of the standardized breakfast start until 4 hours later (T4H30) without subtracting the premeal value, was included in addition to the similar primary endpoint defined as the area under the plasma glucose concentration-time profile from time of the standardized breakfast start until 4 hours later (T4H30) subtracting the premeal value. Moreover, detailed information for timing of metformin administration, if any, and Electrocardiogram were added and discrepancies between sections of the protocol were clarified.
25 January 2013	Change to the inclusion/exclusion criteria for the paediatric population. An upper limit of body mass index for paediatric subjects, that is, 50 kg/m^2 , was added to avoid inclusion of paediatric subjects with extreme obesity in this study. For the paediatric population: male or female subjects were eligible if their T2DM had been diagnosed at least 3 months earlier instead of 1 year at the time of screening. This was to facilitate the recruitment since in the management of T2DM in adolescents and children, therapy should be intensified whenever glucose control was not achieved after 3 to 6 months. For the paediatric population: systolic blood pressure (SBP)/diastolic blood pressure (DBP) levels were too restrictive for obese subjects taking into account the figures presented per age and height percentile. The exclusion would concern children/adolescents with abnormal blood pressure requiring pharmacological treatment as judged by the Investigator. Appendix B "Blood pressure levels by gender, age and height percentile" was consequently removed and the order of appendices following this initial Appendix B was revised and listed in the description of changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported