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Sponsor / Company: Sanofi **Drug substance(s):** Lixisenatide (AVE0010)	**Study Identifiers:** NCT01572649, UTN U1111-1124-3136 & EudraCT 2011-004584-67 **Study code:** PKD11475
Title of the study: 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	
Study center(s): Six centers from 4 countries (pediatric patients from 4 centers in Mexico, South Africa, and the United States [US] and adult patients from 2 centers in the US and United Kingdom)	
Study period: Date first patient enrolled: 24/May/2012 Date last patient completed: 04/Mar/2014	
Phase of development: Phase 1	
Objectives: *Primary objective:* • To investigate the effects of a single subcutaneous (SC) lixisenatide dose of 5 µg and 10 µg 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 pediatric population (10-17 years old) and adults as controls. *Secondary objectives:* To evaluate in both pediatric and adult populations: • Pharmacokinetic (PK) parameters of lixisenatide in plasma after single SC ascending doses. • The maximum PPG excursion and the changes in insulin, C-peptide, and glucagon plasma concentrations following a standardized breakfast. • Safety and tolerability	
Methodology: Multicenter, double-blind, randomized, placebo-controlled, single-dose, 3-period, 3-treatment, 6-sequence crossover study in pediatric and adult patients with type 2 diabetes mellitus (T2DM)	

Number of patients**:** Planned: 12 pediatric patients/12 adult patients

Randomized: 12 pediatric patients/13 adult patients

Treated: 12 pediatric patients/12 adult patients

Evaluated:

Overview of study populations

	Pediatric patients	Adult patients
Number of patients for:		
Evaluable pharmacodynamics population (N)	9[a]	12
Full analysis pharmacodynamics population (N)	12	12
Evaluable pharmacokinetics population (N)	8[b]	10[b]
Full analysis pharmacokinetics population (N)	12	12
Safety population (N)	12	12

a Three patients excluded: 2 patients had vomiting within 4 hours after the standardized meal test and 1 patient ingested only half of the standardized meal test.

b Four pediatric and 2 adult patients excluded: lixisenatide plasma concentrations below lower limit of quantification (LLOQ) in all samples in at least 1 period or no more than 3 consecutive samples above LLOQ in at least 1 period.

Diagnosis and criteria for inclusion:

Male and female patients with T2DM, with or without metformin (at a stable dose for at least 4 weeks prior to randomization); HbA_{1c} ≥7% and ≤10% at screening; fasting C-peptide >0.6 ng/mL at screening; negative test for anti-insulinoma-associated protein and anti-glutamic acid decarboxylase autoantibodies.

Pediatric population: Male and female patients ≥10 and <18 years of age with at least 3 patients below 15 years of age and no more than 3 patients ≥16 and <18 years of age, body mass index (BMI) >85th percentile for age and gender, and BMI ≤50 kg/m^2 (body weight >50 kg)

Adult population: Male and female patients ≥18 and ≤65 years of age, and with BMI >25 kg/m^2 and ≤37 kg/m^2**.**

Study treatments

Investigational medicinal product(s): Lixisenatide and placebo

Formulation: Lixisenatide (100 µg/mL) and placebo, provided as solutions for injection in a 3-mL glass cartridge

Route(s) of administration: SC injection with pen-type injector (OptiClik®)

Dose regimen: In each of the 3 treatment periods, patients were administered, in fasted conditions, a single dose of 5 µg lixisenatide or 10 µg lixisenatide (with 5 µg preceding the 10 µg dose level) or placebo (50 or 100 µL), 30 minutes before a standardized liquid breakfast.

Duration of treatment: Three treatment periods, each lasting 1 day (up to 2 days in case of institutionalization on the evening of Day -1).

Duration of observation: Up to 7 weeks for each patient including a screening period of up to 28 days, 3 treatment periods of up to 2 days each separated by a washout period of 1 to 7 days, and an end-of-study visit 1 to 6 days after the last investigational medicinal product (IMP) administration.

Criteria for evaluation:

Pharmacodynamics:

Primary endpoint:

- Plasma glucose: corrected plasma glucose-$AUC_{0:30h-4:30h}$: area under the curve for plasma glucose concentration-time profile calculated from time of standardized breakfast start (30 minutes after IMP injection and premeal plasma glucose=T0H30) until 4 hours later (T4H30) after subtracting the premeal value (T0H30)

Secondary endpoints:

- PPG-excursion$_{0:30h-4:30h}$: maximum change in PPG from time of standardized breakfast start (30 minutes after IMP injection=T0H30) until 4 hours later (T4H30)
- $AUC_{0:30h-4:30h}$ of plasma glucose, insulin, C-peptide, and glucagon: area under the curve for plasma glucose, insulin, C-peptide or glucagon concentration-time profiles from time of standardized breakfast start (30 minutes after IMP injection=T0H30) until 4 hours later (T4H30)

Safety: Patients were monitored for safety via adverse events (AEs) reported by the patient or noted by the Investigator, physical examination, body temperature, standard clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters.

Pharmacokinetics: Lixisenatide plasma concentration, PK parameters (maximum plasma concentration observed [C_{max}], time to reach C_{max} [t_{max}], area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time [AUC_{last}], area under the plasma concentration versus time curve extrapolated to infinity [AUC], area under the plasma concentration versus time calculated using the trapezoidal method from time T0H30 to T4H30 [$AUC_{0:30h-4:30h}$]).

Pharmacokinetic/Pharmacodynamic sampling times and bioanalytical methods:

Blood samples for pharmacodynamic (PD) analysis were collected at each treatment period for plasma glucose, glucagon, insulin, and C-peptide assessments: blood samples were taken 30 minutes before a standardized breakfast and prior to dosing (T0), then immediately prior to the standardized breakfast (T0H30 hours), and thereafter at T1, T1H30, T2, T2H30, T3H30, and T4H30 (ie, 30, 60, 90, 120, 180, and 240 minutes postbreakfast) for $AUC_{0:30h-4:30h}$ for plasma glucose, glucagon, insulin, and C-peptide measurements.

The quantitative analysis of plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay for glucose from Roche Diagnostics, Mannheim, Germany. The range of the method was 3-1000 mg/dL, with 1 mg/dL as limit of detection (LOD), 3 mg/dL as lower limit of quantification (LLOQ), and 1000 mg/dL as upper limit of quantification.

The method for quantitative analysis for human C-peptide was assessed using the Electro Chemiluminescence Immuno Assay (ECLIA) from Roche Diagnostics, Mannheim, Germany. The range of the method was 0.2-25 ng/mL, with an LLOQ of 0.2 ng/mL and an LOD of 0.07 ng/mL.

The method for quantitative analysis of glucagon was assessed using the radioimmunoassay (RIA) from Euro-Diagnostica, Malmö, Sweden. The range of the method was 4.7-150 pmol/L.

The method for quantitative analysis of insulin was assessed using the ECLIA assay from Roche Diagnostics Deutschland GmbH, Mannheim, Germany. The range of the method was 1-875 mIU/L, with an LLOQ of 1 mIU/L and an LOD of 0.3 mIU/L.

Blood samples for PK analysis were collected at each treatment period for the determination of lixisenatide plasma concentrations: blood samples were taken 30 minutes before a standardized breakfast and prior to dosing (T0), and thereafter at T0H30, T1, T1H30, T2H30, T3H30, T4H30, and T6H30.

Lixisenatide plasma concentrations were determined using a validated double-antibody sandwich enzyme-linked immunosorbent assay method with an LLOQ of 5.5 pg/mL.

Anti-lixisenatide antibody status and, if positive, anti-lixisenatide antibody concentrations were determined using the validated BIAcore technique with a study-specific, and thus not prospectively determined, cutoff as LLOQ. Blood samples were taken only on Day 1/Period 1 before the first IMP administration.

Statistical methods:

Pediatric and adult patients were analyzed separately. Results were compared between the 2 populations descriptively.

Pharmacodynamics:

Within each crossover, the analyses of the primary PD endpoint were performed based on the evaluable PD population, using the full analysis PD population as supportive analyses. Corrected plasma glucose $AUC_{0:30h-4:30h}$ was analyzed using a linear mixed-effect model with sequence, period, and treatment effect as fixed effects, and patient within sequence as random effect, and the T0H30 plasma glucose concentration as covariate. The least square (LS) mean differences between treatment groups and the corresponding 95% confidence intervals (CIs) were estimated within the linear mixed model framework. A significance level of $p<0.05$ was used.

Secondary PD parameters were analyzed using the same statistical model as described above with the corresponding T0H30 values as covariates.

Pharmacokinetics:

The statistical analyses of PK parameters were done on the evaluable PK population, using the full analysis PK population as supportive analyses.

Log-transformed lixisenatide PK parameters C_{max}, $AUC_{last,}$ and $AUC_{0:30h-4:30h}$ were analyzed using a linear mixed-effect model with fixed terms for sequence, treatment and a random term for a patient-within-sequence. Estimates and 90% CIs for the geometric mean ratio of lixisenatide 10 µg versus lixisenatide 5 µg were obtained by computing estimate and 90% CIs for the difference between treatment means within the linear mixed-effects model framework, and then converting to ratio by the antilog transformation to the original scale.

Safety:

The safety analysis was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables and plots if appropriate) by treatment.

Treatment-emergent adverse events (TEAEs) classified in system organ classes (SOCs) and preferred terms were summarized by number and percentage of patients and number of TEAEs. Individual clinical laboratory data, vital signs, and ECG data were listed and flagged for potentially clinically significant abnormalities (PCSAs) and for lower and upper clinical laboratory limits. Frequency of patients with abnormalities and with on-treatment PCSAs were summarized for each type of parameter by treatment.

Summary:

Population characteristics:

Twelve pediatric and 12 adult patients with T2DM were randomized and treated. One additional adult patient was randomized but not treated (this patient withdrew from the study due to personal reasons before the first IMP administration). All patients were on concomitant metformin therapy during the study.

Demographics and baseline characteristics for pediatric and adult patients are summarized in the table below.

Demographics, patient, and disease characteristics at baseline in pediatric and adult patients, safety population

	Pediatric patients	Adult patients
N	12	12
Mean age (years) [min-max]	13.9 [10–17]	51.3 [41–60]
Age group (years) (n, %)		
[10-15]	7 (58.3%)	
[15-16]	2 (16.7%)	
[16-18]	3 (25.0%)	
[18-50]		5 (41.7%)
[50-65]		7 (58.3%)
Sex (n [%])		
Male	6 (50%)	9 (75%)
Female	6 (50%)	3 (25%)
Race (n [%])		
Caucasian/white	1 (8.3%)	6 (50%)
Asian/oriental		1 (8.3%)
Other[a]	11 (91.7%)	5 (41.7%)
Mean weight (kg) [min-max]	84.69 [56.0-129.0]	92.58 [74.7-135.3]
Mean BMI (kg/m^2) [min-max]	31.42 [22.7-44.1]	31.79 [27.0-36.1]
Duration of diabetes (years): median [min-max]	1.56 [0.5-7.9]	4.45 [1.9-20.4]
Duration of metformin treatment (years): median [min-max]	1.56 [0.5-7.6]	2.13 [0.4-7.4]
Mean HbA_{1c} (%) [min-max]	8.65 [7.0-9.9]	8.43 [7.2-9.1]

a Among 11 pediatric patients, 7 self-reported as Hispanic and 4 self-reported as a group of mixed race in South Africa (the Cape Colored). Five adult patients self-reported as Hispanic or Latino.

Pharmacodynamic results:

Primary pharmacodynamic endpoints:

In the pediatric evaluable PD population, the corrected plasma glucose-$AUC_{0:30h-4:30h}$ was decreased by single doses of lixisenatide 5 and 10 µg compared to placebo, but the differences versus placebo were not statistically significant. For the primary endpoint (corrected plasma glucose-$AUC_{0:30h-4:30h}$), the LS mean difference between the lixisenatide 5 µg dose and placebo was -3.92 mmol.h/L; 95% CI: -8.17 to 0.34 mmol.h/L, p=0.0681 (-70.56 mg.h/dL; 95% CI: -147.15 to 6.04 mg.h/dL). The LS mean difference between lixisenatide 10 µg and placebo was -1.52 mmol.h/L; 95% CI: -5.59 to 2.56 mmol.h/L, p=0.4359 (-27.33 mg.h/dL; 95% CI: -100.75 to 46.10 mg.h/dL) (see tables below).

Pediatric patients - plasma glucose premeal corrected $AUC_{0:30h-4:30h}$ (mmol.h/L) per treatment group and difference of lixisenatide 5 µg and 10 µg to placebo - evaluable PD population

Treatment group	N	Least Square Means (SE)[a]		95% CI of difference [mmol.h/L]	p-value
		Corrected plasma glucose-$AUC_{0:30-4:30h}$ [mmol.h/L]	Corrected plasma glucose-$AUC_{0:30-4:30h}$ difference to placebo [mmol.h/L]		
Placebo	9	9.63 (3.95)			
Lixisenatide 5 µg	9	5.72 (3.99)	-3.92 (1.97)	(-8.17; 0.34)	0.0681
Lixisenatide 10 µg	9	8.11 (4.08)	-1.52 (1.89)	(-5.59; 2.56)	0.4359

a SE (standard error)

Pediatric patients - plasma glucose premeal corrected $AUC_{0:30h-4:30h}$ (mg.h/dL) per treatment group and difference of lixisenatide 5 µg and 10 µg to placebo - evaluable PD population

Treatment group	N	Least Square Means (SE)[a]		95% CI of difference [mg.h/dL]	p-value
		Corrected plasma glucose-$AUC_{0:30-4:30h}$ [mg.h/dL]	Corrected plasma glucose-$AUC_{0:30-4:30h}$ difference to placebo [mg.h/dL]		
Placebo	9	173.51 (71.24)			
Lixisenatide 5 µg	9	102.96 (71.81)	-70.56 (35.46)	(-147.15; 6.04)	0.0681
Lixisenatide 10 µg	9	146.19 (73.44)	-27.33 (34.00)	(-100.75; 46.10)	0.4359

a SE (standard error)

In contrast to pediatric patients, in the adult evaluable PD population, single doses of lixisenatide 5 and 10 µg significantly reduced PPG assessed as corrected plasma glucose-$AUC_{0:30h-4:30h}$ compared to placebo. The LS mean difference between lixisenatide 5 µg dose and placebo was -8.57 mmol.h/L; 95% CI: -14.91 to -2.23 mmol.h/L, p=0.0104 (-154.41 mg.h/dL; 95% CI: -268.60 to -40.21 mg.h/dL). The LS mean difference between lixisenatide 10 µg and placebo was -15.48 mmol.h/L; 95% CI: -21.59 to -9.38 mmol.h/L, p<0.0001 (-278.93 mg.h/dL; 95% CI: -388.96 to -168.90 mg.h/dL) (see tables below). The difference between lixisenatide 10 and 5 µg was not statistically significant.

Adult patients - plasma glucose premeal corrected $AUC_{0:30h-4:30h}$ (mmol.h/L) per treatment group and difference of lixisenatide 5 µg and 10 µg to placebo - evaluable PD population

Treatment group	N	Least Square Means (SE)[a]		95% CI of difference [mmol.h/L]	p-value
		Corrected plasma glucose-$AUC_{0:30-4:30h}$ [mmol.h/L]	Corrected plasma glucose-$AUC_{0:30-4:30h}$ difference to placebo [mmol.h/L]		
Placebo	12	16.60 (2.46)			
Lixisenatide 5 µg	12	8.03 (2.95)	-8.57 (3.05)	(-14.91 ; -2.23)	0.0104
Lixisenatide 10 µg	12	1.11 (2.85)	-15.48 (2.93)	(-21.59 ; -9.38)	<0.0001

a SE (standard error)

Adult patients - plasma glucose premeal corrected $AUC_{0:30h-4:30h}$ (mg.h/dL) per treatment group and difference of lixisenatide 5 µg and 10 µg to placebo - evaluable PD population

Treatment group	N	Least Square Means (SE)[a]		95% CI of difference [mg.h/dL]	p-value
		Corrected plasma glucose-$AUC_{0:30-4:30h}$ [mg.h/dL]	Corrected plasma glucose-$AUC_{0:30-4:30h}$ difference to placebo [mg.h/dL]		
Placebo	12	299.01 (44.36)			
Lixisenatide 5 µg	12	144.60 (53.18)	-154.41 (54.99)	(-268.60 ; -40.21)	0.0104
Lixisenatide 10 µg	12	20.08 (51.37)	-278.93 (52.81)	(-388.96 ; -168.90)	<0.0001

a SE (standard error)

Secondary pharmacodynamic endpoints:

In the pediatric evaluable PD population, the results for plasma glucose $AUC_{0:30h-4:30h}$ were consistent with those for the primary endpoint (corrected plasma glucose-$AUC_{0:30h-4:30h}$). Single dose of lixisenatide 5 µg significantly reduced the maximum PPG excursion compared to placebo: the LS mean difference between lixisenatide 5 µg and placebo was –1.50 mmol/L; 95% CI: -2.94 to -0.07 mmol/L, p=0.0415 (-27.08 mg/dL; 95% CI: -52.95 to -1.22 mg/dL). The difference between lixisenatide 10 µg and placebo was not statistically significant: the LS mean difference was -1.13 mmol/L; 95% CI: -2.50 to 0.25 mmol/L, p=0.1005 (-20.30 mg/dL; 95% CI: -45.09 to 4.50 mg/dL).

In the pediatric evaluable PD population, the $AUC_{0:30h-4:30h}$ for glucagon, insulin, and C-peptide were decreased with both lixisenatide 5 and 10 µg compared to placebo except for insulin that increased with lixisenatide 5 µg; however, the variability was high (see tables below). The differences between lixisenatide 5 or 10 µg and placebo were not statistically significant for any of these endpoints, except the decrease in glucagon with lixisenatide 10 µg. No statistically significant differences between lixisenatide doses were observed for any secondary endpoint in the pediatric evaluable PD population.

In the adult evaluable PD population, the results for plasma glucose $AUC_{0:30h-4:30h}$ were consistent with those for the primary endpoint (corrected plasma glucose-$AUC_{0:30h-4:30h}$). Single doses of lixisenatide 5 and 10 µg significantly reduced the maximum PPG excursion during the postprandial period up to 4 hours after the standardized breakfast, compared to placebo. The LS mean difference between lixisenatide 5 µg and placebo was -2.78 mmol/L; 95% CI: -4.29 to -1.27 mmol/L, p=0.0010 (-50.06 mg/dL; 95% CI: -77.27 to -22.86 mg/dL), and the LS mean difference between lixisenatide 10 µg and placebo was -4.32 mmol/L; 95% CI: -5.77 to -2.87 mmol/L, p<0.0001 (-77.85 mg/dL; 95% CI: -103.95 to -51.76 mg/dL).

In the adult evaluable PD population, the $AUC_{0:30h-4:30h}$ for glucagon, insulin, and C-peptide were decreased with both lixisenatide 5 and 10 µg compared to placebo, and these decreases were statistically significant with lixisenatide 10 µg (see table below). The decreases in $AUC_{0:30h-4:30h}$ for glucagon and C-peptide were not statistically significantly different between lixisenatide doses. The decrease in $AUC_{0:30h-4:30h}$ for insulin with lixisenatide 10 µg compared to lixisenatide 5 µg was statistically significant: the LS mean difference was -378.97 pmol.h/L; 95% CI: -711.56 to -46.38 pmol.h/L, p=0.0277 (-63.16 mcIU.h/mL; 95% CI: -118.59 to -7.73 mcIU.h/mL).

Pediatric patients - $AUC_{0:30h-4:30h}$ for plasma glucose, glucagon, insulin, and C-peptide per treatment group and difference between lixisenatide 5 and 10 µg to placebo (SI units) – evaluable PD population

Parameter	Treatment group	N	Least Square Means (SE)[a]		95% CI of difference	p-value
			$AUC_{0:30-4:30h}$	Difference to placebo		
Plasma glucose (mmol.h/L)	Placebo	9	44.50 (3.91)			
	Lixisenatide 5 µg	9	40.53 (3.94)	-3.97 (1.93)	(-8.13 ; 0.19)	0.0599
	Lixisenatide 10 µg	9	42.94 (4.03)	-1.56 (1.85)	(-5.55 ; 2.43)	0.4147
Glucagon (ng.h/L)	Placebo	9	664.83 (19.92)			
	Lixisenatide 5 µg	8	652.63 (22.22)	-12.20 (21.35)	(-58.05 ; 33.65)	0.5769
	Lixisenatide 10 µg	9	621.48 (20.77)	-43.35 (18.30)	(-83.25 ;-3.45)	0.0356
Insulin (pmol.h/L)	Placebo	7	1843.81 (297.88)			
	Lixisenatide 5 µg	8	1973.88 (243.52)	130.07 (372.42)	(-668.69 ; 928.83)	0.7321
	Lixisenatide 10 µg	8	1602.80 (239.93)	-241.01 (365.37)	(-1024.64 ; 542.63)	0.5202
C-peptide (nmol.h/L)	Placebo	8	9.92 (0.56)			
	Lixisenatide 5 µg	8	9.87 (0.59)	-0.04 (0.80)	(-1.79 ;1.71)	0.9565
	Lixisenatide 10 µg	8	9.21 (0.58)	-0.70 (0.74)	(-2.35 ; 0.94)	0.3631

a SE (standard error)

Pediatric patients - $AUC_{0:30h-4:30h}$ for plasma glucose, glucagon, insulin, and C-peptide per treatment group and difference between lixisenatide 5 and 10 µg to placebo (US units) – evaluable PD population

Parameter	Treatment group	N	Least Square Means (SE)[a]		95% CI of difference	p-value
			$AUC_{0:30-4:30h}$	Difference to placebo		
Plasma glucose (mg.h/dL)	Placebo	9	801.63 (70.40)			
	Lixisenatide 5 µg	9	730.11 (70.95)	-71.52 (34.71)	(-146.51; 3.47)	0.0600
	Lixisenatide 10 µg	9	773.58 (72.53)	-28.04 (33.29)	(-99.92; 43.84)	0.4147
Glucagon (pg.h/mL)	Placebo	9	664.83 (19.92)			
	Lixisenatide 5 µg	8	652.63 (22.22)	-12.20 (21.35)	(-58.05; 33.65)	0.5769
	Lixisenatide 10 µg	9	621.48 (20.77)	-43.35 (18.30)	(-83.25; -3.45)	0.0356
Insulin (mcIU.h/mL)	Placebo	7	307.30 (49.65)			
	Lixisenatide 5 µg	8	328.98 (40.59)	21.68 (62.07)	(-111.45; 154.80)	0.7321
	Lixisenatide 10 µg	8	267.13 (39.99)	-40.17 (60.89)	(-170.77; 90.44)	0.5202
C-peptide (ng.h/mL)	Placebo	8	29.78 (1.69)			
	Lixisenatide 5 µg	8	29.65 (1.76)	-0.13 (2.41)	(-5.39; 5.12)	0.9565
	Lixisenatide 10 µg	8	27.67 (1.76)	-2.11 (2.22)	(-7.05; 2.82)	0.3631

a SE (standard error)

Adult patients - $AUC_{0:30h-4:30h}$ for plasma glucose, glucagon, insulin, and C-peptide per treatment group and difference between lixisenatide 5 and 10 µg to placebo (SI units) - evaluable PD population

			Least Square Means (SE)[a]			
Parameter	**Treatment group**	**N**	**$AUC_{0:30-4:30h}$**	**Difference to placebo**	**95% CI of difference**	**p-value**
Plasma glucose (mmol.h/L)	Placebo	12	54.32 (2.46)			
	Lixisenatide 5 µg	12	45.75 (2.95)	-8.57 (3.05)	(-14.91; -2.23)	0.0104
	Lixisenatide 10 µg	12	38.83 (2.85)	-15.48 (2.93)	(-21.59; -9.38)	<0.0001
Glucagon (ng.h/L)	Placebo	12	628.98 (26.47)			
	Lixisenatide 5 µg	12	612.44 (27.90)	-16.54 (18.48)	(-55.53; 22.46)	0.3834
	Lixisenatide 10 µg	12	575.30 (27.95)	-53.68 (18.59)	(-92.89; -14.46)	0.0102
Insulin (pmol.h/L)	Placebo	12	1276.36 (85.63)			
	Lixisenatide 5 µg	11	1181.62 (103.75)	-94.74 (124.99)	(-356.57; 167.09)	0.4579
	Lixisenatide 10 µg	12	802.65 (104.20)	-473.71 (126.74)	(-738.96; -208.45)	0.0014
C-peptide (nmol.h/L)	Placebo	12	8.90 (0.48)			
	Lixisenatide 5 µg	11	8.42 (0.56)	-0.47 (0.64)	(-1.81; 0.87)	0.4701
	Lixisenatide 10 µg	12	6.81 (0.56)	-2.09 (0.63)	(-3.40; -0.77)	0.0036

a SE (standard error)

Adult patients - $AUC_{0:30h-4:30h}$ for plasma glucose, glucagon, insulin, and C-peptide per treatment group and difference between lixisenatide 5 and 10 µg to placebo (US units) - evaluable PD population

			Least Square Means (SE)[a]			
Parameter	**Treatment group**	**N**	**$AUC_{0:30-4:30h}$**	**Difference to placebo**	**95% CI of difference**	**p-value**
Plasma glucose (mg.h/dL)	Placebo	12	978.50 (44.36)			
	Lixisenatide 5 µg	12	824.10 (53.18)	-154.41 (54.99)	(-268.60 ; -40.21)	0.0104
	Lixisenatide 10 µg	12	699.58 (51.37)	-278.93 (52.81)	(-388.96 ; -168.90)	<0.0001
Glucagon (pg.h/mL)	Placebo	12	628.98 (26.47)			
	Lixisenatide 5 µg	12	612.44 (27.90)	-16.54 (18.48)	(-55.53 ; 22.46)	0.3834
	Lixisenatide 10 µg	12	575.30 (27.95)	-53.68 (18.59)	(-92.89 ; -14.46)	0.0102
Insulin (mcIU.h/mL)	Placebo	12	212.73 (14.27)			
	Lixisenatide 5 µg	11	196.94 (17.29)	-15.79 (20.83)	(-59.43 ; 27.85)	0.4579
	Lixisenatide 10 µg	12	133.77 (17.37)	-78.95 (21.12)	(-123.16 ; -34.74)	0.0014
C-peptide (ng.h/mL)	Placebo	12	26.71 (1.45)			
	Lixisenatide 5 µg	11	25.30 (1.69)	-1.42 (1.92)	(-5.43 ; 2.60)	0.4701
	Lixisenatide 10 µg	12	20.45 (1.67)	-6.27 (1.88)	(-10.21 ; -2.32)	0.0036

a SE (standard error)

Pharmacokinetic results:

Lixisenatide plasma concentrations were below LLOQ in all samples from 2 pediatric patients treated with lixisenatide 10 µg and 1 adult patient treated with lixisenatide 5 µg. For 1 pediatric and 1 adult patient treated with lixisenatide 5 µg and 1 pediatric patient treated with lixisenatide 10 µg, no more than 3 consecutive samples were above LLOQ and therefore these patients were not evaluable for PK analysis.

In the pediatric evaluable PK population, the exposure of lixisenatide was similar for both dose groups. A high variability was observed with lixisenatide 10 µg. For C_{max}, the coefficient of variation (CV%) was 47.7% for lixisenatide 5 µg and 74.3% for lixisenatide 10 µg. For AUC_{last}, the CV% was 78.2% for lixisenatide 5 µg and 101.1% for lixisenatide 10 µg. In the pediatric evaluable PK population, the point estimate of the treatment ratio (lixisenatide 10 µg versus lixisenatide 5 µg) for C_{max} was 1.04 (90% CI: 0.71 to 1.51) and for AUC_{last} was 0.88 (90% CI: 0.51 to 1.49).

In the pediatric full PK population, the exposure was slightly higher in patients treated with lixisenatide 10 µg compared to treatment with lixisenatide 5 µg. A high variability was observed for both dose groups. For C_{max}, the coefficient of variation (CV%) was 61.7 for lixisenatide 5 µg and 72.1 for lixisenatide 10 µg. For AUC_{last}, the CV% was 92.5 for lixisenatide 5 µg and 97.4 for lixisenatide 10 µg.

Following single-dose SC administration in adult patients, the exposure of lixisenatide increased with the dose, and was proportional with dose for the evaluable and full PK population.

In pediatric patients, the exposure was similar to that in adults treated with lixisenatide 5 µg, but lower than in adults treated with lixisenatide 10 µg.

Pharmacokinetic parameters for lixisenatide in plasma - evaluable PK populations

Mean ± SD (Geometric Mean) [CV%]	Plasma Lixisenatide			
	Paediatric		Adults	
	Lixisenatide 5 µg	Lixisenatide 10 µg	Lixisenatide 5 µg	Lixisenatide 10 µg
N	8	8	10	10
C_{max} (pg/mL)	29.7 ± 14.2 (26.3) [47.7]	34.3 ± 25.4 (27.2) [74.3]	26.0 ± 15.4 (22.8) [59.4]	56.9 ± 21.3 (53.3) [37.5]
t_{max}[a] (h)	1.25 (0.48 - 3.50)	0.49 (0.48 - 3.55)	1.50 (0.42 - 3.50)	2.50 (0.42 - 3.50)
$t_{1/2z}$ (h)	3.19 ± 1.12 (3.01) [35.1][b]	2.52 ± 0.775 (2.41) [30.8][c]	3.10 ± 1.22 (2.89) [39.3]	2.79 ± 1.35 (2.59) [48.1]
AUC_{last} (pg•h/mL)	99.4 ± 77.7 (76.9) [78.2]	108 ± 109 (67.4) [101.1]	101 ± 58.0 (90.8) [57.3]	242 ± 90.0 (228) [37.2]
$AUC_{0:30h-4:30h}$ (pg•h/mL)	82.5 ± 54.6 (67.4) [66.2][b]	88.0 ± 76.0 (64.3) [86.4][c]	77.2 ± 42.4 (70.0) [54.9]	181 ± 71.9 (168) [39.6]

[a] Median (Min - Max)

evaluable paediatric population subjects: 484001004-006, 484001008, 484001010, 710002001, 710002005, 710002009

[b] N= 7 for subject 710002005 missing could not be calculated

[c] N= 7 for subject 710002009 missing could not be calculated

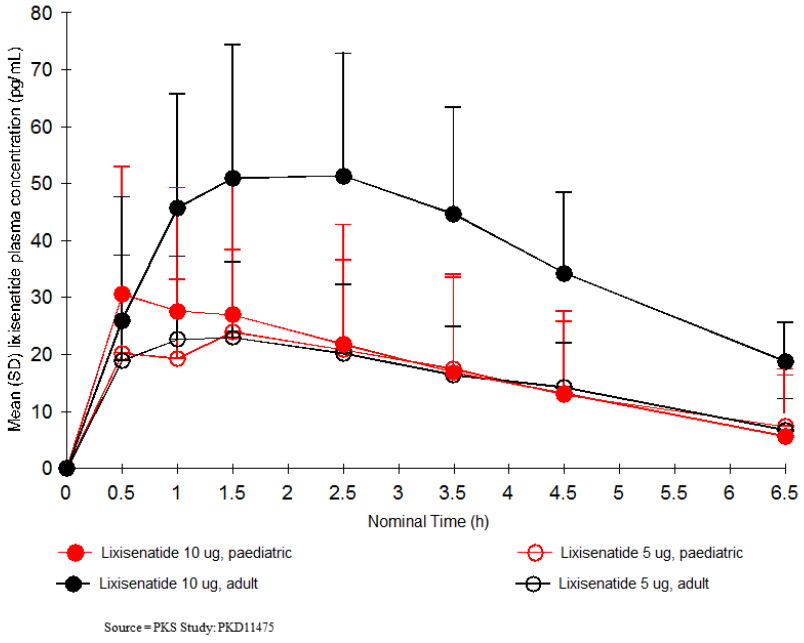
evaluable adult population: subjects 826001004, 826001021, 840005006, 840005010-011, 840005014, 840005016-017, 840005020-021

Source = PKS Study : PKD11475; Scenario: P-D-A-EV-OD, Version 1, P-D-A-EV-OD-E02, Version 3

Point estimates of treatment ratios of lixisenatide 10 µg versus 5 µg – evaluable PK population

Point estimate ratio [90% CI]	Pediatric	Adults
N	8	10
C_{max}	1.04 [0.71 – 1.51]	2.34 [1.85 – 2.95]
AUC_{last}	0.88 [0.51 – 1.49]	2.51 [1.90 – 3.30]
$AUC_{0:30-4:30h}$	0.93 [0.57 – 1.50]	2.41 [1.88 – 3.08]

Mean (+SD) lixisenatide plasma concentrations by treatment (evaluable PK population, linear scale)



Safety results:

No serious AEs were reported during the study, and no patient discontinued the study due to TEAEs. In the pediatric population, 4 patients (1 after injection of placebo, 1 after lixisenatide 5 µg, and 2 after lixisenatide 10 µg) experienced 6 TEAEs (5 from the gastrointestinal disorders SOC and 1 from the infections and infestations SOC). Of these patients, 1 experienced vomiting of mild intensity 43 minutes after injection of placebo (5 minutes after the standardized liquid breakfast), and another patient experienced vomiting of mild intensity with concomitant nausea 3 hours and 15 minutes after injection of lixisenatide 5 µg (2 hours and 31 minutes after the standardized liquid breakfast). One patient experienced diarrhea and concomitant nausea after injection of lixisenatide 10 µg. The incidence of TEAEs was low in the adult population (1 event of diarrhea in 1 placebo-treated patient). All TEAEs were of mild to moderate intensity. All patients recovered without sequelae with or without corrective treatment.

In the pediatric population, there were few PCSAs for blood pressure with no relationship to the IMP or dose administered. Few patients had PCSAs for ECG parameters (prolonged PR, QRS, and QTc) without relevant differences between lixisenatide and placebo.

There were no PCSAs (during the on-treatment period) for blood pressure or ECG parameters in the adult population.

All patients, except 1 adult, were anti-lixisenatide antibody negative at study entry**.**

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