SYNOPSIS

Title of the study: An open-label, randomized, two-arm parallel group study to compare the effects of 4-week QD treatment with lixisenatide or liraglutide on the postprandial plasma glucose in patients with type 2 diabetes not adequately controlled with metformin (PDY10931)

Investigator: [redacted]

Study centers: 7 centers in Germany

Publications (reference): None

Study period:

Date first patient enrolled: 03/Aug/2010

Date last patient completed: 18/Nov/2010 (last contact date: 15/Dec/2010)

Phase of development: Phase 2a

Objectives:

Primary: To investigate the effects of repeated subcutaneous doses of 20 µg lixisenatide as compared to 1.8 mg liraglutide in reducing postprandial plasma glucose (PPG) assessed as area under the plasma glucose concentration curve (AUC) after a standardized breakfast at the end of a 4-week treatment period in patients with type 2 diabetes

Secondary:

- To assess the effects of lixisenatide as compared to liraglutide after a 4-week treatment period in patients with type 2 diabetes:
  - on the maximum PPG excursion, and on the changes in insulin, pro-insulin, C-peptide and glucagon plasma concentrations following a standardized breakfast
  - on the 24-h profile of plasma glucose
  - on HbA_{1c}
  - on satiety markers (obestatin, PYY_{3-36} and oxyntomodulin)
- To assess the clinical and laboratory safety profile of lixisenatide and liraglutide over a 4-week treatment period in patients with type 2 diabetes

Methodology: multicenter, open-label, randomized, 2-arm parallel group study with once-daily dosing during a 4-week treatment period (2-week titration dose and 2-week maintenance dose)

Number of patients:	Planned: 120 (60 in each group)
	Randomized: 148 (77 for lixisenatide and 71 for liraglutide)
	Treated: 148 (77 for lixisenatide and 71 for liraglutide)
Evaluated:	Pharmacodynamic: 143 (75 for lixisenatide and 68 for liraglutide)
	Safety: 148 (77 for lixisenatide and 71 for liraglutide)

Diagnosis and criteria for inclusion: Male and female patients with type 2 diabetes mellitus as defined by the World Health Organization (WHO); fasting plasma glucose ≥7 mmol/L (126 mg/dL) or 2-hour PPG) ≥11.1 mmol/L (200 mg/dL), diagnosed at least 1 year before the screening visit and not adequately controlled by metformin at a dose of at least 1.5 g/day for at least 3 months prior to screening; HbA_{1c} (glycosylated hemoglobin) ≥6.5% and ≤9% at screening

Investigational product: lixisenatide, 100 µg/mL solution for injection in a 3-mL glass cartridge

Dose: 10 µg titration dose; 20 µg maintenance dose

Administration: subcutaneous injection once daily with pen-type injector (OptiClik®), fasted

Batch number: [redacted]

Duration of treatment: 10 µg (titration dose) for 2 weeks followed by 20 µg (maintenance dose) for 2 weeks

Duration of observation: up to 7 weeks for each patient

Comparator therapy: liraglutide, 6 mg/mL solution for injection in a prefilled 3-mL Victoza® pen

Dose: titration doses of 0.6 mg for 1 week followed by 1.2 mg for 1 week; maintenance dose of 1.8 mg for 2 weeks

Administration: subcutaneous injection once daily with Victoza pen, fasted

Batch number: [redacted]

Criteria for evaluation:

Pharmacodynamic:

Primary endpoint: The change from baseline in the area under the corrected (ie, relative to the premeal glucose concentration) plasma glucose concentration-time curve calculated using the linear trapezoidal rule (GLU-$AUC_{0:30-4:30}$), determined from glucose assessments on Day 28 from the time of standardized breakfast start (30 minutes after study medication injection) to 4 hours after breakfast (4:30 hours after study medication injection)

Secondary endpoints:

- Change from baseline in postprandial plasma glucose excursion (maximal postprandial change in plasma glucose) determined from the time of breakfast start (30 minutes after study medication injection) on Day 28 to 4 hours after breakfast (4:30 hours after study medication injection), relative to the premeal plasma glucose concentration
- 24-hour plasma glucose profile at baseline and on Day 28
- Serum pro-insulin, insulin, and C-peptide concentration profiles and glucagon plasma concentration profile on Day -1 and Day 28
- Change from baseline in corrected (ie, relative to the premeal value) $AUC_{0:30-4:30}$ for the postprandial plasma concentrations for pro-insulin, insulin, C-peptide, and glucagon determined from the time of standardized breakfast start (30 minutes after study medication injection) to 4 hours after breakfast (4:30 hours after study medication injection) on Day 28 (7-timepoint profile)
- Change in the pro-insulin to insulin ratio from baseline to Day 28
- Change in HbA_{1c} from baseline to Day 28
- Change in satiety markers (PYY_{3-36}, oxyntomodulin, and obestatin) from time-matched baseline to Day 28

For pharmacodynamic endpoints, pro-insulin, insulin, and C-peptide were assayed in serum whereas glucose, glucagon, PYY_{3-36}, oxyntomodulin, and obestatin were assayed in plasma.

Safety: adverse events reported by the patient or noted by the Investigator; standard hematology and blood chemistry; automatic reading electrocardiogram (ECG), vital signs

Statistical methods

Pharmacodynamics:

The primary pharmacodynamic population was the modified intention-to-treat (mITT) population, which includes all randomized patients who received at least 1 dose of lixisenatide or liraglutide and had both a baseline assessment and at least 1 postbaseline assessment of any primary or secondary pharmacodynamic variable, irrespective of compliance with the study protocol and procedures. All continuous pharmacodynamic parameters including the primary endpoint (changes from baseline to Week 4 in GLU-$AUC_{0:30-4:30h}$) were analyzed using an analysis of variance (ANOVA) model with treatment and center as fixed effects and the baseline value of the corresponding parameter as covariate. Mean estimates (with the corresponding 2-sided 95% confidence interval [CI]) of comparison between lixisenatide and liraglutide were obtained using linear contrasts within the model framework. The statistical test for the primary pharmacodynamic variable was 2-sided at the alpha level of 0.05.

Safety:

Safety analyses for the 4-week randomized treatment period were descriptive and were based on the safety population, defined as all patients randomized and exposed to at least 1 dose of lixisenatide or liraglutide, regardless of the amount of treatment administered. Patients who received treatment different from that assigned by randomization were analyzed according to the treatment received. The safety analysis was based on review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables and plots if appropriate for ECG and vital signs parameters only) by treatment. Treatment-emergent adverse events (TEAEs) classified in system organ classes and preferred terms were tabulated, then 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. The frequency of patients with abnormalities and with PCSAs was summarized for each type of parameter by treatment.

Summary:

A total of 148 patients with type 2 diabetes mellitus (T2DM) were randomized in this study, and 144 completed the 4-week treatment, 75 patients treated with lixisenatide and 69 with liraglutide. Four patients (2 in each treatment group) withdrew from the study due to TEAEs (see Safety results section). Demographics and baseline characteristics were similar between the 2 treatment groups (see table below).

Demographics and patient characteristics at baseline, safety population

	Lixisenatide group	Liraglutide group
N	77	71
Mean Age (years) [min-max]	60.5 [44 – 74]	59.7 [37 – 74]
Sex (n, %)		
Male	49 (63.6%)	50 (70.4%)
Female	28 (36.4%)	21 (29.6%)
Mean BMI (kg/m^2) [min-max]	31.23 [23.3-38.2]	31.33 [21.8-38.5]
Duration of diabetes (years): median [min-max]	6.71 [1.1-30.8]	6.69 [1.1-25.6]
Duration of metformin treatment (years): median [min-max]	5.03 [0.3-16.6]	4.67 [0.3-16.8]

N=number of patients; BMI = body mass index; max = maximum; min = minimum

Pharmacodynamic results:

Primary endpoint

In this 4-week treatment study in patients with T2DM, lixisenatide reduced significantly the corrected plasma glucose $AUC_{0:30-4:30h}$ (h*mg/dL) from baseline: -227.25 compared to -72.83 in the liraglutide group. The estimated mean difference between the 2 treatments was -154.42 [95% CI: -180.30 to -128.54] for lixisenatide versus liraglutide and was statistically significant ($p < 0.0001$) (see table below).

Estimated corrected postmeal plasma glucose $AUC_{0:30-4:30h}$ (h*mg/dL) changes from baseline per treatment group and estimated treatment difference

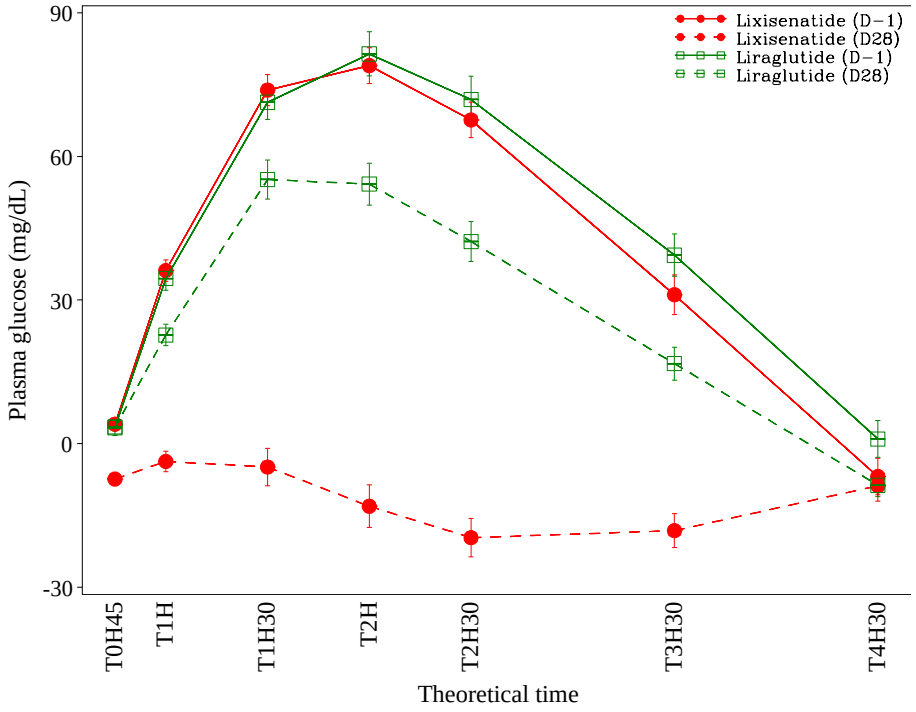
Treatment group	N	Mean (SEM or SE)[a]			95% CI of difference	p-value
		Day -1 corrected AUC0:30-4:30h (baseline)	Estimated corrected AUC0:30-4:30h change from Baseline to Day 28	Estimated lixisenatide versus liraglutide difference		
Lixisenatide	75	169.41 (9.70)	-227.25 (9.93)	-154.42	(-180.30; -128.54)	<0.0001
Liraglutide	68	183.86 (12.24)	-72.83 (10.30)			

a SEM for baseline values and SE for estimated AUC values

AUC = area under the curve; CI = confidence interval; SE = standard error; SEM = standard error of the mean

Lixisenatide reduced the increase in plasma glucose after a standardized breakfast to a much greater extent compared to liraglutide (see figure below).

Mean ±SEM concentrations for postprandial plasma glucose change from premeal values on Day -1 and Day 28 – pharmacodynamic population



Secondary endpoint

There was a substantial modification of PPG excursion at Day 28 in the lixisenatide group, with a significant effect on maximum PPG levels (mg/dL): -70.43 in the lixisenatide group compared to -24.93 in the liraglutide group with a mean treatment difference estimate of -45.50 [95% CI: -55.21 to -35.80] for lixisenatide compared to liraglutide. This difference was statistically significant (p <0.0001).

The number of patients with 2-hour postmeal plasma glucose levels below 140 mg/dL after 4 weeks of treatment (Day 28) was higher in the lixisenatide group (52 patients [69.3%]) than in the liraglutide group (20 patients [29.4%]).

The 24-hour plasma glucose profiles for lixisenatide and liraglutide treatments at Day 28 compared to Day -1 exhibited an overall reduction in plasma glucose (except before dinner at T12h30 in the lixisenatide group), with decreases in the peak glucose levels that occur in response to meal ingestion (in the lixisenatide group).

The changes in the 7-time point profile of free insulin and C-peptide after the meal test were different between the two treatment groups. A decrease in AUC from baseline to Day 28 for free insulin and C-peptide was observed in the lixisenatide group while an increase occurred in the liraglutide group; differences between treatment groups for both parameters were statistically significant (p <0.0001) (see table below). Pro-insulin AUC was decreased in both treatment groups, to a lesser extent in the lixisenatide group. Decreased AUC for glucagon was more pronounced in the lixisenatide group compared to the liraglutide group.

Estimated corrected postmeal $AUC_{0:30-4:30h}$ changes from baseline for pro-insulin, free insulin, C-peptide, and glucagon by treatment group and estimated treatment difference

Parameter	Treatment group	N	Mean (SEM or SE)[a]			95% CI of difference	p-value
			Day -1 corrected $AUC_{0:30-4:30h}$ (baseline)	Estimated corrected $AUC_{0:30-4:30h}$ change value from Baseline to Day 28	Estimated lixisenatide versus liraglutide difference		
Pro-insulin	Lixisenatide	75	5.68 (0.72)	-1.27 (0.55)	1.20	(-0.24; 2.63)	0.1007
(µIU*h/mL)	Liraglutide	68	6.54 (0.66)	-2.47 (0.57)			
Free insulin	Lixisenatide	75	99.55 (5.04)	-64.22 (7.07)	-69.56	(-87.98; -51.14)	<0.0001
(µIU*h/mL)	Liraglutide	68	93.24 (6.95)	5.34 (7.33)			
C-peptide	Lixisenatide	75	10.61 (0.51)	-5.03 (0.66)	-6.07	(-7.78; -4.35)	<0.0001
(ng*h/mL)	Liraglutide	68	9.99 (0.59)	1.04 (0.68)			
Glucagon	Lixisenatide	75	27.10 (6.99)	-46.71 (7.52)	-21.24	(-41.02; -1.86)	0.032
(pg*h/mL)	Liraglutide	68	16.47 (9.58)	-25.28 (7.77)			

a SEM for baseline values and SE for estimated AUC values

N=number of patients; AUC = area under the curve; CI = confidence interval; SE = standard error; SEM = standard error of the mean

The ratio pro-insulin to free insulin was slightly decreased on Day 28 before the test meal, with a similar decrease in both groups (mean change before the meal test was -0.07 and -0.06 in the lixisenatide and liraglutide groups, respectively) and few changes over time after the meal test were reported in either group at each timepoint.

Mean HbA_{1c} levels decreased in both treatment groups, from 7.20% and 7.41% (baseline) to 6.89% and 6.92% (at Day 28) in the lixisenatide and liraglutide groups, respectively. The estimated treatment difference for the change from baseline was 0.14% (lixisenatide versus liraglutide, $p < 0.01$).

Safety results:

No deaths or SAEs occurred during the study. Four (4) patients (2 in each treatment group) discontinued the study due to TEAEs, coded as preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA version 13.1). In the lixisenatide group, a site injection rash (after the challenge test on Day 16) occurred 1 day after a transient drug eruption in 1 patient, and a drug hypersensitivity reaction appeared on Day 21 in another patient. Only these 2 reactions (drug eruption and drug hypersensitivity) were adjudicated as allergic reactions possibly related to the study medication by the Allergic Reaction Assessment Committee (ARAC); they were diagnosed by ARAC as urticaria and angiooedema, respectively. The site injection rash was diagnosed as a local reaction at the injection site by ARAC. In the liraglutide group, study drug administration was stopped on Day 11/ 12 in 2 patients due to diarrhea of severe intensity associated with abdominal cramps and pain in 1 patient (later diagnosed with Crohn's disease) and due to moderate nausea and mild dyspepsia in the other patient.

No hypoglycemia and no pancreatitis were reported in any group during the study.

The incidence of TEAEs was lower in the lixisenatide group compared to the liraglutide group (58.4% versus 73.2%), mainly related to an imbalance in decreased appetite, gastrointestinal events (diarrhea, abdominal distension, and upper abdominal pain) and nervous system disorders (dizziness). The most commonly reported TEAEs (>10% in one or both treatment groups) were decreased appetite, nausea, dyspepsia, diarrhea, headache, abdominal distencion, back pain, and vomiting.

Conclusions: [redacted]

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