SYNOPSIS

Title of the study: A randomized, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week double-blind treatment period assessing the efficacy and safety of lixisenatide in patients with Type 2 diabetes insufficiently controlled with insulin glargine and metformin (EFC10781).
Coordinating Investigator: [redacted]
Study center: Multicenter (140 centers in 25 countries)
Publications (reference): Not applicable
Study period: Date first patient enrolled: 13 October 2009 Date last patient completed: 01 August 2011
Phase of development: Phase 3
Objectives: Primary Objective The primary objective of this study was to assess the effects on glycemic control of lixisenatide in comparison to placebo as an add-on treatment to insulin glargine and metformin in terms of HbA_{1c} change over a period of 24 weeks. Secondary Objectives • Assess the effects of lixisenatide on: - The percentage of patients reaching HbA_{1c} <7% or ≤6.5% - Plasma glucose (fasting, postprandial during a standardized meal challenge test, 7-point self monitored profiles) - Body weight - Insulin glargine doses • Evaluate lixisenatide safety and tolerability (including anti-lixisenatide antibody assessment) as add-on treatment to insulin glargine and metformin • Assess the impact of lixisenatide on treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (state) (DTSQs) in participating countries where it is validated.

Methodology: Randomized, multicenter, double-blind, placebo-controlled, 2-arm parallel group study. The study comprised 3 periods:

- An up-to 14-week screening period, which included an up to 2-week screening phase and a 12-week run-in phase with introduction and titration of insulin glargine on top of metformin ± thiazolidinediones (TZDs). Insulin glargine was administered with a treat-to-target regimen to achieve a fasting plasma glucose (FPG) target between 80 mg/dL (4.4 mmol/L) and 100 mg/dL (5.6 mol/L).
- A 24-week double-blind treatment period: at the end of the run-in, patients whose HbA_{1c} was ≥7% and ≤9%, and mean fasting self-measured plasma glucose (SMPG) calculated from the self measurements over the 7 days prior to Visit 12 (Week -1) was ≤140 mg/dL (7.8 mmol/L), were randomized (1:1) to receive either lixisenatide or placebo in addition to insulin glargine in combination with metformin ±TZDs. After randomization, lixisenatide or the volume matching placebo started with a daily dose of 10 µg for 1 week, then increased to 15 µg for 1 week followed by the maintenance dose of 20 µg up to the end of the treatment period. Insulin glargine dose modification/titration was permitted in both treatment groups to maintain the FPG target during the 24-week double-blind treatment phase.
- A 3-day safety follow up period

Number of patients:	Planned: 450	Randomized: 446	Treated: 446
Evaluated:	Efficacy: 446	Safety: 446	Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion: Patients with type-2 diabetes mellitus (T2DM), diagnosed for at least 1 year at the time of the screening visit, insufficiently controlled with stable doses of metformin ≥ 1.5 g/day or a combination of stable doses of metformin ≥ 1.5 g/day with sulfonylureas (SUs) or glinides [that were to be discontinued at the run-in start] and/or TZDs; and HbA_{1c} ≥7% and ≤10% at screening.

Study treatments

Investigational medicinal products (IMPs): lixisenatide (300 µg) solution for injection in a 3-mL glass cartridge (ie, 100 µg/mL) or volume-matched placebo; insulin glargine (Lantus® SoloSTAR® pen) solution for injection (300 units).

Formulation:

Lixisenatide: 3-mL aqueous solution (in cartridge) containing the active ingredient, 300 µg (ie, 100 µg/mL), glycerol, sodium acetate trihydrate, methionine, metacresol, hydrochloric acid, sodium hydroxide, water for injection

Placebo**:** 3-mL aqueous solution (in cartridge).

Route of administration: subcutaneous injection (with the OptiClik® self-injector device for lixisenatide or placebo or with SoloSTAR® pen for insulin glargine)

Dose regimen:

The starting dose per injection was 10 µg of lixisenatide or volume-matched placebo administered once daily within 1 hour before breakfast. The dose per injection was increased after 1 week to 15 µg, and after 1 more week from 15 to 20 µg, provided safety and tolerability did not prevent further dose increase, up to a maximum level of 20 µg/injection of lixisenatide or volume-matched placebo from Week 2 onwards throughout the entire study for all patients.

Insulin glargine was administered once daily before breakfast (simultaneously to lixisenatide or placebo during the 24-week double-blind treatment period). Insulin dosage was adjusted throughout the study to achieve a FPG target between 80 mg/dL (4.4 mmol/L) and 100 mg/dL (5.6 mol/L).

Batch numbers: [redacted]

Duration of treatment: 24 weeks

Duration of observation: 39 weeks ± 7 days

Criteria for evaluation:

Efficacy: Efficacy was assessed using the following criteria: the absolute change in HbA_{1c} from baseline to Week 24; the percentage of patients with HbA_{1c} <7% or ≤6.5% at Week 24; the changes in 2-hour postprandial plasma glucose (PPG) and glucose excursion (2-hour PPG - plasma glucose [30 minutes prior to the meal test before study drug administration] during a standardized meal), 7-point SMPG profiles, body weight, FPG,
average daily insulin glargine dose, and in treatment satisfaction score from baseline to Week 24; the percentage of patients requiring rescue therapy during the 24-week treatment period.

Safety: Adverse events and serious adverse events (SAEs) (including in particular, symptomatic and severe symptomatic hypoglycemia, local intolerability at injection site, allergic or allergic-like reactions, suspected pancreatitis and major cardiovascular events), vital signs (blood pressure, heart rate), electrocardiograms (ECG), clinical laboratory (including in particular amylase, lipase and calcitonin).

Anti-drug antibody assessments: The status and concentration of anti-lixisenatide antibodies were determined at baseline, and at Weeks 2, 4, and 24; crossreactivity with endogeneous glucagon-like peptide 1 (GLP-1) or glucagon at Week 24; samples for the antibody assessment were also taken before the start of rescue therapy and at end of treatment, if the end of treatment visit occurred before Week 24. The samples were taken in the morning, before the injection of the IMP. The antibodies to human insulin were determined at the start of the run-in period (Week-12) and the antibodies to insulin glargine were determined at the start of the run-in period (Week-12) and at Weeks 0 (randomization) and 24.

Pharmacokinetics: Not Applicable.

Statistical methods:

Efficacy: The efficacy of lixisenatide was assessed using the modified intent-to-treat population (mITT), which consisted of all patients who were randomized (analyzed "as randomized"), received at least 1 dose of double-blind IMP, and had both a baseline assessment and at least 1 post baseline assessment of any primary or secondary efficacy variable, irrespective of compliance with the study protocol and procedures. The baseline for efficacy variables was defined as the last available value prior to the first injection of the IMP (lixisenatide or placebo).

The primary efficacy endpoint (the absolute change in HbA_{1c} from baseline to Week 24) was analyzed using an analysis of covariance (ANCOVA) model with treatment groups (lixisenatide and placebo), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%] and TZD use [yes, no]), and country as fixed effects, and using the baseline HbA_{1c} as a covariate.

A stepwise testing procedure was applied in order to ensure control of type 1 error. Provided the primary endpoint was shown to be statistically significant at $\alpha = 0.05$, the testing procedure was performed to test the secondary efficacy variables (change in 2-hour PPG after a standardized meal from baseline to Week 24; change in the average of the 7-point SMPG, body weight, average daily insulin glargine dose and FPG from baseline to Week 24; and the percentage of patients requiring rescue therapy during the 24-week double-blind treatment period). The tests stopped as soon as an endpoint was found not statistically significant at $\alpha = 0.05$. No multiplicity adjustment was made on the other secondary efficacy variables, which are not mentioned above.

Similar to the approach used for the primary endpoint, data for all continuous secondary efficacy endpoints were analyzed using the previously described ANCOVA model with the corresponding baseline value as a covariate. Data of the categorical secondary efficacy endpoints (ie, percentage of patients with HbA_{1c} <7.0% or with HbA_1c ≤6.5% [HbA_{1c} responders] at Week 24, and percentage of patients requiring rescue therapy during the 24-week treatment period) were analyzed using a Cochran-Mantel-Haenszel method.

Safety: The safety population was the total treated population, defined as all patients randomized and exposed to at least 1 dose of the double-blind IMP (lixisenatide or placebo), regardless of the amount of treatment administered. The evaluation of AEs, clinical laboratory data, vital signs, and ECG data was descriptive.

Immunogenicity assessments: Data concerning anti-lixisenatide antibody status, concentration and crossreactivity with endogeneous GLP-1 or glucagon, and the biologically active concentration of lixisenatide were listed and summarized using descriptive statistics. Data concerning anti-insulin glargine and anti human insulin antibody status and titer were listed and summarized using descriptive statistics.

Summary:

A total of 950 patients were planned for enrolment into the run-in period in order to be able to randomize 450 patients. Of 898 patients who were enrolled, 446 patients were eligible at the end of the run-in and were randomized (223 in each treatment group). All randomized patients were exposed to the randomized treatment and included in the analyses.

Population characteristics: The demography and patients' baseline characteristics were generally similar across the 2 randomized treatment groups for the safety population. The median patient age was 57.0 years (56.0 years for lixisenatide and 57.0 years for placebo). The majority of patients were Caucasian (74.4%). Both genders were equally represented. At baseline, 53.8% of patients were obese with a median body mass index of 30.71 kg/m^2.

Efficacy results:

In the randomized patients who had uncontrolled T2DM while on oral anti-diabetic treatment(s) prior to enrolment, addition and titration of insulin glargine during the 12-week run-in resulted in a reduction in the mean HbA_{1c} value from 8.6% to 7.6% (7.56% for lixisenatide and 7.60% placebo). After randomization, the addition of lixisenatide led to a further significantly greater HbA_{1c} decrease to a mean value of 6.96% compared with 7.28 % with the placebo treatment (LS mean change of -0.71% and -0.40% in the lixisenatide and placebo groups, respectively). Superiority of lixisenatide compared with placebo was thus demonstrated, based on the predefined primary analysis of the LS mean changes from baseline to Week 24 in HbA_{1c} (LS mean difference for lixisenatide versus placebo of -0.32%; 95% CI: -0.463, -0.171; p<0.0001). This superiority of lixisenatide over placebo was achieved under the circumstance that the insulin glargine dose adjustment to maintain fasting plasma glucose at target (80 - 100 mg/dL [4.4 – 5.6 mmol/L]) was permitted and executed in both treatment groups during the 24-week treatment period. The reduction in HbA_{1c} at Week 24 was similar in antibody-positive and antibody-negative patients.

At Week 24, the percentage of patients attaining the glycemic goal of HbA_{1c} ≤6.5% or <7%, was also significantly higher in the lixisenatide group as compared with the placebo group (p<0.0001 for HbA_{1c} ≤6.5% and p = 0.0001 for HbA_{1c} <7%).

Treatment with lixisenatide significantly improved postprandial glycemic control as measured by 2-hour PPG and postprandial glucose excursion. A statistically significant reduction in 2-hour PPG after a standard breakfast test-meal from baseline to Week 24 was achieved in the lixisenatide group compared with the placebo group, with a LS mean difference of -3.16 mmol/L (p<0.0001). Correspondingly, a substantial reduction in glucose excursion after this test meal was observed in the patients treated with lixisenatide compared with those treated with placebo (LS mean difference for lixisenatide versus placebo of -3.09 mmol/L, 95% CI: -3.842, -2.331).

Furthermore, treatment with lixisenatide led to a statistically significant improvement in the average of the 7-point SMPG profile compared with the placebo group (LS mean difference versus placebo of -0.39 mmol/L; p = 0.0071).

A statistically significant difference in the body weight change from baseline was found between the 2 treatment groups: body weight remained almost unchanged in the lixisenatide group and increased in the placebo group (LS mean body weight change from baseline to Week 24 of 0.28 kg and 1.16 kg, respectively; LS mean difference for lixisenatide versus placebo was -0.89 kg; 95% CI: -1.423, -0.353; p = 0.0012).

Over the 24-week on-treatment period, in both groups, the daily insulin dose increased gradually which was permitted by the protocol to maintain FPGs between 80 and 100 mg/dL (4.4 and 5.6 mmol/L) (LS mean change from baseline was 3.10 U in the lixisenatide group and 5.34 U in the placebo group). However, patients in the lixisenatide group showed a significantly less increase in daily insulin glargine dose while achieving a greater reduction in HbA_{1c} (LS mean difference for lixisenatide versus placebo of -2.24 U; p = 0.0300).

For fasting plasma glucose, no statistically significant difference was observed between treatment groups (LS mean difference for lixisenatide versus placebo of -0.12 mmol/L; p = 0.5142) which can be explained by the fact that in both groups, insulin glargine was optimally titrated to a target FPG. A total of 2 patients (1 [0.4%] in each group) received a rescue therapy.

Safety results:

An overview of the safety results observed during the whole study is provided in the following table. The proportion of patients who experienced treatment-emergent adverse events (TEAEs) was higher in the lixisenatide treated group (79.8%) compared with that in the placebo group (68.2%). The disproportion of TEAE was largely driven by the TEAEs from the gastrointestinal disorders system organ class (SOC) (39.9% for lixisenatide versus 16.1% for placebo), mainly nausea and vomiting, which is consistent with the known safety profile of GLP-1 receptor agonists.

	Placebo (N=223)	Lixisenatide (N=223)
Patients with any TEAE	152 (68.2%)	178 (79.8%)
Patients with any serious TEAE	10 (4.5%)	17 (7.6%)
Patients with any TEAE leading to death	2 (0.9%)	0
Patients with any TEAE leading to permanent treatment discontinuation	8 (3.6%)	19 (8.5%)

TEAE: Treatment Emergent Adverse Event
n (%) = number and percentage of patients with at least one adverse event
Note: On-treatment period = the time from the first dose of double-blind study medication up to 3 days after the last dose administration.

Two patients on placebo had TEAEs (myocardial infarction and multiple myeloma) leading to death during the treatment period while no fatal TEAEs occurred in the lixisenatide group.

The percentage of patients who experienced serious TEAEs was greater in the lixisenatide group (17 patients [7.6%]) than in the placebo group (10 patients [4.5%]). However, the serious TEAEs distributed over a variety of SOCs without a notable increase in any specific SOCs.

The percentage of patients with TEAEs leading to treatment discontinuation was 8.5% (19 patients) in the lixisenatide group compared with 3.6% (8 patients) in the placebo group. The most common TEAEs leading to treatment discontinuation were TEAEs from the gastrointestinal disorders SOC, mainly nausea and vomiting symptoms reported in 9 (4.0 %) lixisenatide-treated patients versus no patient on placebo. The most common reason for treatment discontinuation in the placebo group was TEAEs from the cardiac disorders SOC (3 patients [1.3%] versus 1 patient [0.4%] for lixisenatide).

During the on-treatment period, 50 (22.4%) lixisenatide-treated patients reported at least one symptomatic hypoglycemic event fulfilling the protocol definition compared with 30 (13.5%) patients for placebo. The symptomatic hypoglycemic event rate (number of events per patient-year) was greater in the lixisenatide group (0.9 events per patient-year) than that in the placebo group (0.5 events per patient-year). The increase in hypoglycemic events in the lixisenatide group was noticed mainly during the first 6 weeks of treatment (including the 3-week dose increase period) and the event occurrences became similar between the 2 treatment groups later in the treatment period. One severe event was reported with lixisenatide treatment and none with placebo. The investigator reported the severe event during lixisenatide treatment as a serious TEAE possibly related to the IMP and suggested that delay of a meal (skipped lunch) might be an alternative explanation for the event.

Injection site reactions were reported in 15 patients (6.7%) in the lixisenatide group and 5 patients (2.2%) in the placebo group. None of the events were serious and they were all considered to be of either mild or moderate intensity by the Investigator. Two patients (0.9%) in the lixisenatide group (and none in the placebo group) had an injection site related TEAE leading to treatment discontinuation.

Four patients (3 patients [1.3%] in the lixisenatide and 1 patient [0.4%] in the placebo group) had a TEAE adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee, of which 2 events of urticaria from the lixisenatide group and 1 event of dermatitis from the placebo group were adjudicated as possibly related to the IMP. Of these 2 events of urticaria in the lixisenatide group, 1 led to permanent treatment discontinuation.

In total, 15 patients reported TEAEs of either increases in pancreatic enzymes (lipase and/or amylase) or pancreatitis on the electronic case report form (eCRF) AE form specific for “suspected pancreatitis”: 5 patients (2.2%) in the lixisenatide group and 10 patients (4.5%) in the placebo group. Of these TEAEs, 1 TEAE of lipase increased leading to IMP discontinuation and 1 TEAE of pancreatitis were reported in the placebo group (versus none on lixisenatide). The event of suspected pancreatitis (asymptomatic) was reported at the end of treatment (Week 24); the patient had two preceding non treatment-emergent AEs of elevations in blood amylase and lipase during the run-in period. The Investigator assessed the suspected pancreatitis as possibly related to the IMP.

Two patients (0.9%) in the placebo group, but no patient in the lixisenatide group, experienced a TEAE of blood calcitonin increased reported in the pre-specified AE form for increased calcitonin (≥ 20 ng/L).

The percentage of patients with a TEAE of coronary artery disorders was low and similar between the lixisenatide group (5 patients [2.2%]) and the placebo group (4 patients [1.8%]). For 1 patient (0.4%) in the placebo group, the coronary artery disorder TEAE (myocardial infarction) considered as not related to IMP, was serious and led to permanent discontinuation of the IMP and subsequent death.

At baseline, 11 patients (5.0%) in the lixisenatide group and 10 patients (4.6%) in the placebo group were already antibody-positive to lixisenatide. The percentage of patients who were antibody-positive in the lixisenatide group increased with time, to a maximum of 66.8% (127 of 190 patients) at Week 24. The biologically active concentration of lixisenatide (predose) at Week 24 was above 40 pg/mL (lower limit of quantification) in 68 of the 124 samples with a positive antibody status in the lixisenatide group, with a median of 121.600 pg/mL.

The anti-lixisenatide antibodies had no cross-reactivity with endogenous GLP-1 as well as with glucagon.

The percentage of lixisenatide-treated patients with antibody-positive status who experienced TEAEs during the on-treatment period was 80.5% as compared with 79.5% in antibody-negative patients. Overall, there was no substantial difference in the TEAE profile between the antibody-positive and antibody-negative populations.

At start of the run-in phase (Week -12), in the placebo and the lixisenatide groups, 1.4% of the patients had a positive anti human-insulin (or anti-status, and 1.8% of the patients had a positive status for anti insulin-glargine antibodies. During the study the percentage of patients being positive for anti insulin-glargine antibodies increased in both groups up to 10.9% and 6.8% in the lixisenatide and placebo groups, respectively, on Day 1 before randomization to lixisenatide or placebo and up to 16.6% and 11.8 % in the lixisenatide and placebo groups respectively at Week 24.

The vital signs data and the assessment of ECG readings did not reveal any specific safety concerns. Slight and similar decreases in diastolic blood pressure and slight and similar increases in heart rate were observed in both treatment groups.

Pharmacokinetic results: Not Applicable.

Conclusions: [redacted]

Date of report: 16-Dec-2014