# SYNOPSIS

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| Title of the study: | EFC12261: A 24-week, open-label, randomized, 2-arm parallel group, multinational, multi-center clinical trial to compare the efficacy and safety of lixisenatide injected prior to the main meal of the day versus lixisenatide injected prior to breakfast in type 2 diabetic patients not adequately controlled on metformin |
| Investigator(s): | [redacted] |
| Study center(s): | 77 centers |
| Publications (reference): | NA |
| Study period: | |
| Date first patient enrolled: | 15-Feb-2012 |
| Date last patient completed: | 14-May-2013 |
| Phase of development: | Phase 3 |

Objectives:

Primary Objective

To demonstrate non inferiority of lixisenatide injected prior to the main meal of the day versus lixisenatide injected prior to breakfast in terms of HbA1c reduction from baseline to week 24, in type 2 diabetic patients not adequately controlled on metformin.

Secondary Objective(s)

The secondary objectives were to assess the effect of the 2 lixisenatide regimens on:

The percentage of patients who:

- reached the target of HbA1c <7% at week 24
- reached the target of HbA1c $\leq$6.5% at week 24
- reached the target of HbA1c <7% at week 24 and did not experience confirmed (plasma glucose (PG) <60mg/dL) symptomatic hypoglycemia during the 24-week treatment period
- reached the target of HbA1c <7% and had no weight gain at week 24
- reached the target of HbA1c <7% and had no weight gain at week 24 and did not experience confirmed (PG <60mg/dL) symptomatic hypoglycemia during the 24-week treatment period
- reached the target of HbA1c <7% and have a 2-h PPG <140 mg/dL after breakfast or main meal (depending on treatment group) at week 24

7-point Self-Monitored Plasma Glucose (SMPG) profiles

Fasting Plasma Glucose (FPG)

Body weight

Treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (state) (DTSQs) in the participating countries where it is validated

To assess safety and tolerability of both lixisenatide regimens.

Methodology: Open-label, 1:1 randomized, active-controlled, 2-arm, parallel-group multicenter study comparing:

- Lixisenatide injected within 1 hour prior to the main meal of the day (breakfast, lunch or dinner)
- Lixisenatide injected within 1 hour prior to breakfast

The patients were stratified:

- by main meal of the day (breakfast, lunch or dinner defined at visit 2, based on the patient's answer to the question "On most days, at which meal do you eat the largest amount of food?") and
- by screening values of HbA1c (<8%, ≥8%).

Number of patients: Planned: 400

Randomized: 451

Treated: 451

Completed the study: 391

Evaluated:

Efficacy: 450

Safety: 451

Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus diagnosed for at least 1 year, treated with metformin at a stable dose of at least 1.5 g/day for at least 3 months prior to screening visit, and with HbA1c ≥7% and ≤10% at screening.

Study treatments

Investigational medicinal product(s): lixisenatide (AVE0010)

Formulation: lixisenatide was supplied as a sterile aqueous solution for subcutaneous (SC) injection in a 3-mL glass cartridge containing 300 µg of the active ingredient (ie, 100 µg/mL), Glycerol, Sodium acetate trihydrate, Methionine, Metacresol, HCL/NaOH, water for injection.

Route(s) of administration: Lixisenatide was injected subcutaneously using the re-usable OptiClik® self-injector device

Dose regimen: Metformin was to be kept at stable dose throughout the study unless there was a specific safety issue related to this treatment.

Batch number(s): [redacted]

Noninvestigational medicinal product(s) (if applicable): metformin

Formulation: metformin ≥1.5 g/day.

Route(s) of administration: Oral

Dose regimen: metformin was to be kept at stable dose throughout the study unless there was a specific safety issue related to this treatment.

Batch number(s): not applicable

Duration of treatment: 24 weeks

Duration of observation: up to approximately 28 weeks

Criteria for evaluation:

Efficacy:

Primary Endpoint:

- Change in HbA1c from baseline to Week 24

Secondary Endpoint(s):

- Percentage of patients reaching HbA1c <7 % at week 24
- Percentage of patients reaching HbA1c ≤6.5 % at week 24
- Percentage of patients reaching HbA1c <7% at week 24 and not experiencing confirmed (plasma glucose [PG] <60mg/dL) symptomatic hypoglycemia during the 24-week treatment period
- Percentage of patients reaching HbA1c <7% and having no weight gain at week 24
- Percentage of patients reaching the target of HbA1c <7% and having no weight gain at week 24 and not experiencing confirmed (PG <60mg/dL) symptomatic hypoglycemia during the 24-week treatment period
- Percentage of patients reaching HbA1c < 7% and having a 2-h PPG <140mg/dL after breakfast or main meal (depending on the treatment group) at week 24
- Change in 7-point SMPG profiles from baseline to week 24 (each time point and mean daily value)
- Change in FPG from baseline to week 24
- Change in body weight from baseline to week 24
- Change in treatment satisfaction from baseline to week 24 (each individual item from DTSQs and treatment satisfaction score calculated as sum of items 1, 4, 5, 6, 7 and 8)

Safety:

Adverse events, serious adverse events, symptomatic hypoglycemia, vital signs, safety laboratory values.

Symptomatic hypoglycemia was defined in the protocol as an event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying plasma glucose <60 mg/dL (3.3 mmol/L) or associated with prompt recovery after oral carbohydrate if no plasma glucose measurement was available.

Additional endpoints were assessed using Continuous Glucose Monitoring (CGM) in a sub-study performed in some selected sites. Sub-study report provided separately.

Pharmacokinetics: Not applicable

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Not applicable

Statistical methods:

Efficacy: The statistical test for the primary efficacy endpoint (change in HbA1c from baseline to week 24) was one-sided, with alpha level of 0.025 and using a non-inferiority margin of 0.4% HbA1c.

The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model with treatment (lixisenatide prior to the main meal of the day or lixisenatide prior to breakfast), randomization strata of main meal of the day (breakfast, lunch, dinner), randomization strata of screening HbA1c (<8%, ≥8%) and country as fixed effects and using the baseline HbA1c value as a covariate. The baseline value was defined as the last available value prior to the first dose administration of study treatment. Difference between treatment groups and two-sided 95% confidence interval was estimated within the framework of the above ANCOVA model.

Non-inferiority would be demonstrated if the upper bound of the two-sided 95%CI of the difference between lixisenatide injected prior to the main meal of the day and lixisenatide injected prior to breakfast on modified intention-to-treat (mITT) population was ≤ 0.4%.

If non-inferiority was established, then a corresponding check of statistical superiority of lixisenatide injected prior to the main meal of the day over lixisenatide injected prior to breakfast would be performed for the primary endpoint.

All continuous secondary efficacy endpoints were analyzed using the same ANCOVA model as described for the primary endpoint. Differences between treatment groups and confidence intervals were estimated within the framework of ANCOVA.

For 7-point SMPG profiles, values at each visit were averaged across the two profiles performed in the week before the visit. The mean daily (ie, averaged over 7 points) SMPG change from baseline to week 24 was analyzed. In addition, the SMPG change from baseline to week 24 for each of the 7 points was evaluated, respectively

All categorical efficacy parameters was analyzed by using Cochran-Mantel-Haenszel (CMH) method stratified by randomization strata of main meal of the day (breakfast, lunch, dinner) and randomization strata of screening HbA1c (<8%, ≥8 %).

Safety: Safety analyses for the 24-week open-label treatment period were descriptive, based on the safety population. Treatment-emergent adverse events (TEAEs) were defined as adverse events ( AEs) that developed or worsened or became serious during the period from the administration of first dose of the study treatment (lixisenatide prior to the main meal of the day or lixisenatide prior to breakfast) in the open-label period up to 3 days after the last administration.

CGM sub-study

Analysis of data from the CGM sub-study was detailed in a specific separate statistical analysis plan. CGM results will be reported separately.

Summary:

Population characteristics: There were 451 patients randomized (225 to the lixisenatide main meal group and 226 to the lixisenatide breakfast group), and all were exposed to the study treatment with 450 patients included in the mITT population. Demography and baseline characteristics were generally similar across the treatment groups. The median age was 58 years. The study population was primarily Caucasian (93.6%). When defined at Visit 2 by the response to the question "on most days, at which meal do you eat the largest amount of food", the main meal of the day was breakfast for 8.2% of patients, lunch for 53.0% of patients and dinner for 38.8% of patients. When defined after an interview with a dietician, the percentages were similar 10.2% (breakfast), 53.5% (lunch), and 36.3% (dinner) as main meal of the day.

Efficacy results:

The EFC12261 study results demonstrate that lixisenatide administered before the main meal (breakfast, lunch or dinner) is non-inferior to lixisenatide administered before breakfast, in type 2 diabetes mellitus (T2DM) patients inadequately controlled on metformin alone. This conclusion is based on the primary endpoint, LS mean change in HbA1c from baseline to week 24: the values were -0.65% for the main meal group and -0.74% for the breakfast group (LS mean difference versus breakfast group = 0.09%, 95% CI: -0.067% to 0.242%), the upper bound of the two-sided 95% CI was less than the predefined non-inferiority margin of 0.4%. Sensitivity analyses, including the MMRM analysis, also corroborated this finding. Further, statistical superiority of the main meal group over breakfast group was not demonstrated (LS mean difference versus. breakfast group = 0.09%, p-value = 0.2664).

Overall results of the subgroup analyses of the primary endpoint were consistent for gender, baseline HbA1c and main meal of the day. However some differences in HbA1c were found depending on the age group, body mass index (BMI) and country. In whatever subgroup, lixisenatide administered before breakfast or before the main meal relevantly reduced HbA1c.

A similar percentage of patients in each group reached target HbA1c ≤6.5% (22.5% versus 25.7%) or <7 % (43.6% versus 42.8%) respectively for the main meal group and the breakfast group.

In the secondary endpoints, FPG and body weight reductions were similar in the two groups, as were results for composite endpoints such as percentage of patients with HbA1c <7% without symptomatic documented hypoglycemia, percentage of patients with HbA1c < 7% without weight gain, percentage of patients with HbA1c <7% without symptomatic documented hypoglycemia and no weight gain, and percentage of patients with HbA1c <7% and 2h-PPG <140 mg/dL at the end of treatment.

The 7-point SMPG profiles for the main meal and breakfast groups both showed improvements between baseline and Week 24; the profiles within the main meal group were different according to which was the patient's main meal (breakfast, lunch or dinner). The greatest reduction in post-prandial glucose levels between baseline and week 24 were demonstrated for the meal following the administration of lixisenatide: post-breakfast for the breakfast subgroup, post-lunch for the lunch subgroup, and post-dinner for the dinner subgroup, with a residual effect seen on the subsequent meals.

In conclusion, lixisenatide whether administered before breakfast or before the main meal of the day provides effective treatment for patients with T2DM inadequately controlled on metformin alone.

Safety results:

Lixisenatide, either before the main meal of the day or before breakfast, was well tolerated. Slightly fewer patients reported TEAEs in the lixisenatide main meal group (125 [55.6%]) than in the breakfast group (135 [59.7%]). The most frequently reported TEAE in both groups was nausea (33 [14.7%] in the main meal group and 35 [15.5%] in the breakfast group).

Seven patients (3.1%) in the main meal group and 7 (3.1%) patients in the breakfast group had treatment emergent SAEs, distributed over a variety of system organ classes (SOCs) without a particular increase in any specific SOC. One patient (lixisenatide main meal group) died during study due to pancreatic carcinoma (post-treatment AE). Ten patients (4.4%) in the main meal group discontinued treatment due to TEAEs compared with 11 (4.9%) patients in the breakfast group: for 8 of these patients (4 [1.8%] in each group) TEAEs leading to treatment discontinuation were from the gastrointestinal disorders SOC.

Symptomatic hypoglycemia was observed in 13 patients (5.8%) and 5 patients (2.2%) for the main meal and breakfast groups respectively; in some cases, the episodes of hypoglycemia were associated with a skipped meal or unanticipated physical exercise. In the main meal group this was the case for 13/29 events in 10 patients; in the breakfast group, there were 4/6 such events in 4 patients. No severe symptomatic hypoglycemia was reported in either group.

Two patients (1 [0.4%] in main meal group and 1 [0.4%] in the breakfast group) reported 2 events (urticaria and asthma respectively) that were positively adjudicated as allergic reactions by the Allergic Reaction Assessment Committee (ARAC). Neither event was adjudicated as possibly related to the investigational medicinal product.

There were 21 patients (9 patients (4.0%) in the main meal group and 12 (5.3%) patients in the breakfast group) who experienced injection site reactions. None of these was considered serious or severe, or led to treatment discontinuation.

Four patients (1.8%) in the main meal group and 3 (1.3%) in the breakfast group had TEAE of lipase increased (>2 x ULN) reported on a specific adverse event form, none was accompanied with clinical symptoms. Six patients (2.7%) in the main meal group and 3 patients (1.3%) in the breakfast group had at least 1 value of lipase ≥3 x ULN during the treatment period.

No TEAE of pancreatitis was reported in the study.

Two patients in the breakfast group and none in the main meal group had a TEAE of increased calcitonin or hypercalcitoninemia (≥20 pg/mL [ng/L]) that were reported on the specific AE form. For these 2 patients calcitonin levels were already greater than 20 pg/ml on Day 1 of the study.

In conclusion, lixisenatide administered either before the main meal of the day or before breakfast was well tolerated with little difference between the groups. The safety profile in both groups was consistent with the known safety profile of lixisenatide, and with GLP-1 receptor agonists in general. Nausea was the most frequently reported adverse event in both groups with an incidence of approximately 15%. The incidence of symptomatic hypoglycemia (according to protocol definition) was low in both treatment groups: 5.8% in the main meal group and 2.2% in the breakfast group.

Pharmacokinetic results: Not applicable

Conclusions: [redacted]

Date of report: 23-Jan-2015