SYNOPSIS

Title of the study: A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of AVE0010 on top of a sulfonylurea in patients with type 2 diabetes not adequately controlled with sulfonylurea (EFC6015)

Investigator(s): [redacted]

Study center(s): Multicenter (136 centers in 16 countries)

Publications (reference): Not applicable.

Study period:

Date first patient enrolled: 08/Jul/2008

Date last patient completed: 14/Jan/2011

Phase of development: 3

Objectives:

Primary: To assess the effects of AVE0010 (hereinafter referred to by the international nonproprietary name, lixisenatide) on glycemic control in comparison to placebo as an add-on treatment to sulfonylurea, with or without metformin, in terms of absolute glycosylated hemoglobin (HbA_{1c}) reduction over a period of 24 weeks in patients with type 2 diabetes.

Secondary:

- To assess the effects of lixisenatide on:
  - Percentage of patients reaching HbA_{1c} <7% or HbA_{1c} ≤6.5%,
  - Body weight,
  - Fasting plasma glucose (FPG),
  - β-cell function assessed by homeostasis model assessment-(HOMA)-β,
  - 2-hour postprandial plasma glucose (PPG), glucagon, insulin, proinsulin, and C-peptide after a standardized meal challenge test in a substudy in all patients in selected centers (approximately 30% of all randomized patients);
- To assess the safety and tolerability of lixisenatide;
- To assess lixisenatide pharmacokinetics (PK) and anti-lixisenatide antibody development.

Methodology: This was a randomized, double-blind, placebo-controlled, 2-arm, unbalanced design, parallel-group study with a 2-step titration regimen (10 μg once daily [QD] for 1 week, then 15 μg QD for 1 week, followed by the maintenance dose of 20 μg QD). The study was double-blind with regard to active and placebo treatments; however, the study drug volume (ie, dose of active drug or matching placebo) was not blinded.

Number of patients:	Planned:	855	Randomized:	859	Treated:	859
Evaluated:	Efficacy:	856	Safety:	859	Pharmacokinetics:	845

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus (T2DM) diagnosed at least 1 year before the screening visit, insufficiently controlled with a sulfonylurea alone (at a stable dose for at least 3 months prior to screening) or a sulfonylurea in association with metformin (at a stable dose of at least 1.5 g/day [except at least 0.75 g/day in Japan and 1.0 g/day in South Korea] for at least 3 months prior to screening); and HbA_{1c} ≥7.0% and ≤10% at screening.

Investigational product: lixisenatide

Dose: 10 μg, 15 μg, and 20 μg

Administration: subcutaneous injection

Batch number(s): [redacted]

Duration of treatment: At least 76 weeks (24 weeks main double-blind treatment; variable double-blind extension)

Duration of observation: Approximate minimum duration of 79 weeks (up to 2 weeks screening + 1 week run-in + 24 weeks main double-blind treatment + variable extension + 3 days follow-up)

Reference therapy: placebo

Dose: 10 μg, 15 μg, and 20 μg

Administration: subcutaneous injection

Batch number(s): [redacted]

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 body weight and FPG from baseline to Week 24, the change in 2-hour PPG and glucose excursion after a standardized meal from baseline to Week 24, the change in glucagon, plasma insulin, proinsulin, proinsulin-to-insulin ratio, and C-peptide under fasting conditions and 2 hours after a standardized meal from baseline to Week 24, the change in β-cell function assessed by HOMA-β from baseline to Week 24, the percentage of patients requiring rescue therapy during the main 24-week period, and the percentage of patients with ≥5% weight loss from baseline to Week 24.

Safety: Safety was assessed by review of adverse events (AEs) and in particular treatment-emergent adverse events (TEAEs), occurrence of symptomatic hypoglycemia, clinical laboratory data, vital signs, and electrocardiogram (ECG) data.

Anti-lixisenatide antibody assessments: The status and concentration of anti-lixisenatide antibodies were determined at baseline, and at Weeks 2, 4, 24, 76, and 100; samples were also taken at end of treatment, if the end of treatment visit occurred before Week 76. The samples were taken in the morning, before the injection of the investigational product. The cross-reactivity of the antibodies with endogenous glucagon-like peptide 1 (GLP-1) and glucagon was determined at the main study endpoint (Week 24).

Pharmacokinetics: Samples for assessment of plasma concentrations of lixisenatide were taken at Weeks 2, 24, 76, and 100; samples were also taken before the start of rescue therapy and at end of treatment, if the end of treatment visit occurred before Week 76. Samples were taken once prior to injection of the investigational product and then once within 1 to 4 hours postinjection. In vitro active concentration of lixisenatide was also determined (predose), at the times mentioned for the total concentration of lixisenatide, plus at Week 4.

Statistical methods:

Efficacy: The efficacy of lixisenatide was assessed using the modified intent-to-treat population, which consisted of all patients who were randomized (analyzed "as randomized"), received at least 1 dose of double-blind investigational product, 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 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 (lixisenatide or placebo), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%], and screening metformin 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 that 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 FPG and body weight from baseline to Week 24, change in β-cell function assessed by HOMA-β from baseline to Week 24, and percentage of patients requiring rescue therapy during the main 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 for other secondary efficacy variables other than those 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 for 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 (CMH) method. Results for all efficacy endpoints during the variable extension period and at the end of treatment were to be evaluated by descriptive statistics only.

Safety: The safety population was the total treated population, defined as all patients randomized and exposed to at least 1 dose of the investigational product, regardless of the amount of treatment administered. The evaluation of AEs, clinical laboratory data, vital signs, and ECG data was descriptive.

Anti-lixisenatide antibodies: Data concerning anti-lixisenatide antibody status and concentration, and concerning cross-reactivity of the antibodies with endogenous GLP-1 and glucagon were listed and summarized using descriptive statistics.

Pharmacokinetics: Individual plasma concentrations of lixisenatide and the biologically active concentration of lixisenatide were summarized using descriptive statistics.

Summary:

Efficacy results:

The demographic and patient baseline characteristics were generally similar between the 2 treatment groups for the safety population. Overall, 134 patients (15.6%) were receiving sulfonylurea only and 725 patients (84.4%) were receiving both sulfonylurea and metformin at the screening visit, and this was similar among both treatment groups.

The efficacy of lixisenatide versus placebo was demonstrated based on the prespecified primary analysis of the least square (LS) mean changes from baseline to Week 24 in HbA_{1c} (-0.85% and -0.10% in the lixisenatide and placebo groups, respectively; LS mean difference versus placebo was -0.74%; 95% confidence interval [CI]: -0.867, -0.621; p<0.0001). The reduction in HbA_{1c} was similar in antibody-positive and antibody-negative patients.

The analysis of HbA_{1c} responders (ie, patients with HbA_{1c} ≤6.5 or <7% at Week 24) using the CMH method also showed a significant treatment difference versus placebo for the lixisenatide group. At Week 24, 19.3% of lixisenatide-treated patients and 4.7% of placebo-treated patients had achieved HbA_{1c} values ≤6.5%; 36.4% of patients in the lixisenatide group and 13.5% of patients in the placebo group had achieved HbA_{1c} values <7%.

For 2-hour PPG after a standardized meal, the LS mean change from baseline to Week 24 was -6.19 mmol/L for the lixisenatide group and -0.21 mmol/L for the placebo group (LS mean difference versus placebo was -5.98 mmol/L; 95% CI: -6.912, -5.043; p<0.0001). The analysis of glucose excursion showed similar results.

For FPG, the LS mean change from baseline to Week 24 was a decrease of -0.99 mmol/L for the lixisenatide group and -0.36 mmol/L for the placebo group (LS mean difference versus placebo was -0.63 mmol/L; 95% CI: -0.919, -0.346; p<0.0001).

The LS mean body weight loss from baseline at Week 24 was 1.76 kg for the lixisenatide-treated patients and 0.93 kg for the placebo-treated patients (LS mean difference versus placebo was -0.84 kg; 95% CI: -1.250, -0.421; p<0.0001).

The percentage of patients requiring rescue therapy during the main 24-week treatment period was significantly lower for the lixisenatide group compared with placebo (3-fold fewer patients with lixisenatide: 23 patients [4.0%] in the lixisenatide group and 36 patients [12.6%] in the placebo group; p<0.0001) without an adjustment for multiplicity.

The results of the standardized meal challenge test were as follows: in patients treated with lixisenatide, decreases from baseline to Week 24 in fasting and 2-hour postprandial glucagon, fasting and 2-hour postprandial plasma insulin, and fasting and 2-hour postprandial proinsulin were observed, with significant differences versus placebo in all 2-hour postprandial parameters. These reductions were maintained during the extension period. There was a comparable decrease from baseline to Week 24 in the fasting proinsulin-to-insulin ratio, and in fasting C-peptide in patients treated with lixisenatide and placebo, which was maintained during the extension period. The 2-hour postprandial C-peptide decreased slightly more in lixisenatide-treated patients compared with placebo.

For HOMA-β, a median increase of 4.37 for the lixisenatide group compared with -0.33 for the placebo group was observed, with no statistically significant difference between treatment groups according to the prespecified parametric analysis (LS mean difference versus placebo was -1.80; 95% CI: -12.424, 8.819; p = 0.7387). A sensitivity analysis using a nonparametric model showed a statistically significant difference for lixisenatide versus placebo (p = 0.0011).

The clinically beneficial effects on the efficacy variables (HbA_{1c}, FPG, 2-hour PPG, and body weight) observed during the main 24-week treatment period were maintained during the variable extension period.

Safety results:

An overview of the safety results observed during the whole study is provided in the following table. Two patients in the lixisenatide group had TEAEs leading to death. Ninety-three patients had serious TEAEs, with a similar incidence rate in the lixisenatide and placebo groups (10.1% and 12.3%, respectively). During the whole study, 177 patients (30.9%) in the lixisenatide group and 82 patients (28.7%) in the placebo group prematurely discontinued study treatment; the percentage of patients with TEAEs leading to treatment discontinuation was higher in the lixisenatide group compared with the placebo group (12.4% in the lixisenatide group compared with 7.7% in the placebo group). The most common TEAE leading to permanent treatment discontinuation was nausea in the lixisenatide group (24 patients [4.2%]). The corresponding number of patients (%) in the placebo group was 1 (0.4%). During the main 24-week treatment period, 74 patients (12.9%) in the lixisenatide group and 31 patients (10.8%) in the placebo group prematurely discontinued study treatment; the percentage of patients with TEAEs leading to treatment discontinuation was 56 (9.8%) in the lixisenatide group and 14 (4.9%) in the placebo group.

	Placebo (N=285)	**Lixisenatide (N=574)**
Patients with any TEAE	216 (75.8%)	468 (81.5%)
Patients with any serious TEAE	35 (12.3%)	58 (10.1%)
Patients with any TEAE leading to death	0	2 (0.3%)
Patients with any TEAE leading to permanent treatment discontinuation	22 (7.7%)	71 (12.4%)

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

A slightly higher number of patients in the lixisenatide-treated group experienced TEAEs compared to the placebo-treated group (81.5% and 75.8%, respectively), which was mainly related to an imbalance in the gastrointestinal disorders system organ class. The most commonly reported TEAE in the lixisenatide group was nausea, which is consistent with the known safety profile of GLP-1 receptor agonists. A higher percentage of patients had nausea and vomiting in the lixisenatide treatment group compared with the placebo treatment group (nausea: 161 patients [28.0%] and 25 patients [8.8%], respectively; vomiting: 61 patients [10.6%] and 15 patients [5.3%], respectively).

In total, 178 patients had symptomatic hypoglycemia fulfilling the protocol definition during the study; the number of patients with symptomatic hypoglycemia in the lixisenatide treatment group was 127 patients (22.1%) and 51 patients (17.9%) in the placebo treatment group. The number of events per 100 patient years was lower in the lixisenatide group (46.9) compared with the placebo group (56.0). Symptomatic hypoglycemia with blood glucose <60 mg/dL was reported for 111 patients (19.3%) in the lixisenatide group compared with 43 patients (15.1%) in the placebo group; the number of events per 100 patient years was lower in the lixisenatide group (39.9) compared with the placebo group (51.4). Two (0.3%) lixisenatide-treated patients had severe symptomatic hypoglycemia events per protocol definition during the on-treatment period for the whole study, whereas 1 (0.4%) placebo-treated patient had severe symptomatic hypoglycemia during the same period.

Injection site reactions were reported for 28 patients (4.9%) in the lixisenatide treatment group and for 8 patients (2.8%) in the placebo treatment group, none of which were serious or were considered to be severe in intensity by the Investigator; 3 of the patients (0.5%) in the lixisenatide group permanently discontinued study treatment due to an event of injection site reaction.

Twelve patients (11 patients [1.9%] and 1 patient [0.4%] in the lixisenatide and placebo treatment groups, respectively) had a TEAE adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee (ARAC), out of which 1 event (local reaction) in a lixisenatide-treated patient was considered to be related to investigational product by the ARAC. In the lixisenatide treatment group, there were 2 patients with serious TEAEs adjudicated as anaphylactic shock per ARAC assessment (allergy to arthropod sting [which did not lead to treatment discontinuation] and anaphylactic shock following intravenous application of an antibiotic drug [after the patient had already discontinued treatment]); neither event was considered related to study treatment by the ARAC or the Investigator.

Fifteen patients (2.6%) in the lixisenatide treatment group and 9 patients (3.2%) in the placebo treatment group had events of changes in pancreatic enzymes, lipase, or amylase reported on the electronic case report form AE form specific for "suspected pancreatitis". There were 7 confirmed cases of pancreatitis in 7 patients (0.8%) according to the local gastroenterologist and/or local imaging assessments (out of these 7 patients, 5 patients [0.9%] were in the lixisenatide treatment group [1 pancreatitis, 2 acute pancreatitis, and 2 chronic pancreatitis cases] and 2 patients [0.7%] were in the placebo treatment group [1 acute pancreatitis and 1 responsive pancreatitis cases]).

Eight patients (1.4%) in the lixisenatide treatment group and 5 patients (1.8%) in the placebo treatment group had a TEAE of blood calcitonin increased (calcitonin levels ≥20 ng/L; 1 patient in the lixisenatide group had a value <20 ng/L), of which 1 in the lixisenatide group was serious. For 1 patient in the lixisenatide group, a TEAE of thyroid C-cell hyperplasia was reported, which became serious after treatment discontinuation.

The number of patients with cardiac disorder TEAEs was similar in the 2 treatment groups (34 patients [5.9%] in the lixisenatide group and 12 patients [4.2%] in the placebo group).

The overall incidence rate of potentially clinically significant abnormalities) (PCSAs) for hematology, lipid parameters, pancreatic enzymes, creatinine, uric acid, and liver function tests was generally similar in the 2 treatment groups.

At baseline, 34 patients (6.7%) treated with lixisenatide and 5 patients (2.0%) treated with placebo were already antibody-positive. The percentage of antibody-positive patients in the lixisenatide group increased with time: 215 patients (62.3%) at Week 24 and 261 patients (77.2%) after 76 weeks of lixisenatide treatment; thereafter, the percentage appeared to decrease (79 patients [71.2%] at Week 100).

The antibody concentration was observed to be < the lower limit of quantification (LLOQ; 3.21 nmol/L) in more than half of antibody-positive patients in the lixisenatide group at baseline and at Week 2. At Week 4, in 90/149 (60.4 %) of the antibody-positive observations, the antibody concentration was >LLOQ (median: 16.050 nmol/L); at the later times, the antibody concentration in average decreased and was <LLOQ in more than half of the observations (190/284 at Week 24; 147/239 at Week 76; and 40/79 at Week 100).

Cross-reactivity of the antibodies with endogenous glucagon-like peptide 1, as well as glucagon, was not seen in any of the patients.

Overall, there was no substantial difference in the TEAE profile between the antibody-positive and antibody-negative populations.

The vital signs data and the assessment of ECG readings did not reveal any specific safety signal. Slight and similar decreases in systolic and diastolic blood pressure were observed in both treatment groups. There were minimal changes in heart rate from baseline to the last treatment value in both treatment groups.

Pharmacokinetic results:

The median postinjection concentration of lixisenatide for anti-lixisenatide antibody-negative patients treated with 20 μg/day lixisenatide was 65.35 pg/mL, 70.90 pg/mL, 64.30 pg/mL, and 110.50 pg/mL at Weeks 2, 24, 76, and 100, respectively. The respective medians at predose were below the LLOQ at Weeks 2, 24, and 76, and 15.50 pg/mL at Week 100.

In antibody-positive patients, these values increased remarkably with the duration of treatment: from 83.20 pg/mL at Week 2, to 299.0 pg/mL (Week 24), to 462.5 pg/mL (Week 76), and to 383.0 pg/mL (Week 100). The respective median at predose was <LLOQ at Week 2, and increased to 149.0 pg/mL (Week 24), to 185.0 pg/mL (Week 76), and to 206.0 pg/mL (Week 100). The biologically active concentration (predose) was >LLOQ for >40% of the patients at Week 24 and Week 76. In 88 of 198 antibody-positive patients at Week 24 and 108 of 251 antibody-positive patients at Week 76, a median of 97.85 pg/mL and 120.45 pg/mL, respectively, was determined for the active concentration; the median of the resulting active fraction (active lixisenatide/total lixisenatide) was 0.269 (Week 24) and 0.185 (Week 76).

Conclusions: [redacted]

Date of report: 2-Dec-2014