SYNOPSIS

Title of the study: A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin (EFC6016)

Investigator(s): [redacted]

Study center(s): Multicenter (111 centers in 15 countries)

Publications (reference): Not applicable.

Study period:

Date first patient enrolled: 29/Jul/2008

Date last patient completed: 08/Feb/2011

Phase of development: 3

Objectives:

Primary: To assess the efficacy of AVE0010 (hereinafter referred to by the international nonproprietary name, lixisenatide) on glycemic control in comparison to placebo as an add-on treatment to basal insulin in type 2 diabetes patients treated with basal insulin in terms of absolute glycosylated hemoglobin (HbA_{1c}) reduction over a period of 24 weeks.

Secondary:

- To assess the effects of lixisenatide on:
  - Body weight,
  - 2-hour postprandial plasma glucose (PPG) after standardized meal challenge test,
  - Percentage of patients reaching HbA_{1c} <7%,
  - Percentage of patients reaching HbA_{1c} ≤6.5%,
  - Fasting plasma glucose (FPG),
  - Change in 7-point self-monitored plasma glucose (SMPG) profiles,
  - Change in basal insulin and total insulin doses;
- To assess lixisenatide safety and tolerability;
- To assess lixisenatide pharmacokinetics (PK);
- To assess 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 was not blinded.

Number of patients:	Planned:	450	Randomized:	496	Treated:	495
Evaluated:	Efficacy:	493	Safety:	495	PK:	482

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus (T2DM diagnosed at least 1 year before the screening visit; insufficiently controlled with basal insulin at a stable dose (±20%) of at least 30 U/day for at least 2 months prior to screening; and HbA_{1c} ≥7% 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 double-blind 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, 2-hour PPG (after a standardized meal), glucose excursion (2-hour PPG - plasma glucose [30 minutes prior to the meal test before study drug administration] after a standardized meal), FPG, 7-point SMPG profiles, and in basal insulin and total insulin dose from baseline to Week 24; and the percentage of patients requiring rescue therapy during the main 24-week period.

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 before the start of rescue therapy and 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.

Pharmacokinetics: Samples for assessment of plasma concentrations of lixisenatide were taken on 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. In vitro active concentration of lixisenatide was also determined. 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 Week 24.

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 groups (lixisenatide and placebo), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%] and metformin use at screening [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, FPG, and body weight from baseline to Week 24; and the 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 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 for some 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. Results of 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 double-blind 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 antibody assessments: Data concerning anti-lixisenatide antibody status and concentration 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*:**

Superiority of lixisenatide compared with placebo was demonstrated, based on the predefined primary analysis of the least squares (LS) mean changes from baseline to Week 24 in HbA_{1c} (LS mean change of -0.74% and -0.38% in the lixisenatide and placebo treatment groups, respectively). The LS mean difference for lixisenatide versus placebo was -0.36% ($p = 0.0002$). At Week 24, the percentage of patients considered to be responders, with HbA_{1c} ≤6.5% or <7%, was also significantly higher in the lixisenatide treatment group (44 patients [14.5%] for HbA_{1c} ≤6.5% and 86 patients [28.3%] for HbA_{1c} <7%) versus the placebo treatment group (6 patients [3.8%] for HbA_{1c} ≤6.5% and 19 patients [12.0%] for HbA_{1c} <7%) ($p = 0.0003$ for HbA_{1c} ≤6.5% and $p<0.0001$ for HbA_{1c} <7%). The reduction in HbA_{1c} at Week 24 was similar in antibody-positive and antibody-negative patients.

For 2-hour PPG after a standardized meal, the LS mean change from baseline to Week 24 was greater in the lixisenatide treatment group compared with the placebo treatment group (-5.54 mmol/L and -1.72 mmol/L, respectively); the LS mean difference between the 2 treatment groups (-3.81 mmol/L) was statistically significant (95% confidence interval [CI]: -4.699, -2.925; $p<0.0001$). Furthermore, the LS mean change from baseline to Week 24 in glucose excursion was also greater in the lixisenatide treatment group compared with the placebo treatment group (-4.14 mmol/L and -0.34 mmol/L, respectively), and the LS mean difference between the 2 treatment groups was -3.80 mmol/L (95% CI: -4.572, -3.031).

Treatment with lixisenatide improved the average 7-point SMPG profiles compared with placebo (LS mean change from baseline to Week 24 was -1.49 mmol/L and -0.61 mmol/L, respectively) and the LS mean difference between the 2 treatment groups was statistically significant (-0.88 mmol/L; 95% CI: -1.312, -0.449; $p<0.0001$). A greater LS mean decrease was seen in the lixisenatide treatment group compared with the placebo treatment group at all time points; the greatest LS mean difference between the 2 treatment groups (lixisenatide versus placebo) was seen at 2-hours postbreakfast (-2.37 mmol/L) and the smallest LS mean difference was seen at prebreakfast (-0.30 mmol/L).

A modest and similar decrease in FPG from baseline to Week 24 was observed in both treatment groups (LS mean change of -0.63 mmol/L and -0.55 mmol/L in the lixisenatide and placebo treatment groups, respectively); the treatment difference was not statistically significant (-0.08 mmol/L; 95% CI: -0.590, 0.430; $p = 0.7579$). These results should be considered in parallel with the greater decrease in daily basal insulin dose in the lixisenatide treatment group compared with the placebo treatment group, as described below.

The LS mean body weight loss from baseline at Week 24 was greater for lixisenatide-treated patients (-1.80 kg) than for placebo-treated patients (-0.52 kg); the LS mean difference versus placebo was -1.28 kg (95% CI: -1.803, -0.747).

The percentage of patients requiring rescue therapy during the main 24-week treatment period was small and similar in the 2 treatment groups (5.8% and 7.2% in the lixisenatide and placebo treatment groups, respectively). The percentage of patients requiring rescue therapy over the whole treatment period was lower in the lixisenatide treatment group (29.7%) than in the placebo treatment group (41.6%).

A greater LS mean decrease in daily basal insulin dose from baseline to Week 24 was reported in the lixisenatide treatment group (-5.62 U) compared with the placebo treatment group (-1.93 U), and the LS mean difference between the 2 treatment groups (lixisenatide versus placebo) was -3.69 U (95% CI: -6.568, -0.815). The same results were seen for the daily total insulin dose.

The beneficial effects on the efficacy variables (HbA1c, 2-hour PPG, glucose excursion, 7-point SMPG, body weight, and daily insulin dose) 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. Four patients (2 patients in each treatment group) had TEAEs leading to death. Sixty-three patients had serious TEAEs, with a slightly higher frequency in the lixisenatide treatment group compared with the placebo treatment group (14.0% and 10.2%, respectively). The percentage of patients with TEAEs leading to permanent treatment discontinuation was also slightly higher in the lixisenatide treatment group compared with the placebo treatment group (10.7% and 7.2%, respectively). The most common TEAE leading to permanent treatment discontinuation was nausea in the lixisenatide treatment group (11 patients [3.4%] in the lixisenatide treatment group and no patients in the placebo treatment group); no individual TEAE (by preferred term) leading to discontinuation was reported by more than 2 patients in the placebo treatment group. Similar results were seen for the 24-week treatment period.

	Placebo (N=167)	**Lixisenatide (N=328)**
Patients with any TEAE	143 (85.6%)	287 (87.5%)
Patients with any serious TEAE	17 (10.2%)	46 (14.0%)
Patients with any TEAE leading to death	2 (1.2%)	2 (0.6%)
Patients with any TEAE leading to permanent treatment discontinuation	12 (7.2%)	35 (10.7%)

TEAE: Treatment emergent adverse event.
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.
n (%) = number and percentage of patients with at least one adverse event.

The proportion of patients who experienced TEAEs during the whole study was generally comparable between the lixisenatide-treated and placebo-treated groups (87.5% and 85.6%, respectively). The most commonly reported TEAE was hypoglycemia in both treatment groups (42.1% in the lixisenatide treatment group and 40.7% in the placebo treatment group); nausea was also commonly reported in the lixisenatide treatment group (96 patients [29.3%] in the lixisenatide treatment group and 16 patients [9.6%] in the placebo treatment group), which is consistent with the known safety profile of glucagon-like peptide 1 receptor agonists. Nasopharyngitis was the second most common TEAE in the placebo treatment group (32 patients [9.8%] in the lixisenatide treatment group and 21 patients [12.6%] in the placebo treatment group). A higher percentage of patients in the lixisenatide treatment group (73.5%) had TEAEs during the main 24-week treatment period compared with the placebo treatment group (68.3%); this slight imbalance can be largely attributed to the higher frequency of gastrointestinal disorder TEAEs in the lixisenatide treatment group.

The percentage of patients who had symptomatic hypoglycemia fulfilling the protocol definition during the study was similar in the 2 treatment groups (138 patients [42.1%] in the lixisenatide treatment group and 65 patients [38.9%] in the placebo treatment group). In addition, the number of hypoglycemic events per 100 patient years was similar in lixisenatide treatment group (179.3 events) compared with the placebo treatment group (182.9 events). Seven lixisenatide-treated patients (2.1%) had 8 severe symptomatic hypoglycemia events, per protocol definition, and 1 placebo-treated patient (0.6%) had 1 severe symptomatic hypoglycemia event. One of these severe hypoglycemic events was a serious TEAE (placebo treatment group); none of the other events was serious and none of the events of symptomatic hypoglycemia led to discontinuation of study treatment. During the on-treatment period for the whole study, the number of patients with symptomatic hypoglycemia per protocol definition in the lixisenatide group, and for whom the anti-lixisenatide status was known, was 117 patients (49.4%) and 21 patients (26.9%) for anti-lixisenatide positive and negative patients, respectively as compared to 65 patients (38.9%) in the placebo group.

Injection site reactions were reported for 8 patients (2.4%) in the lixisenatide treatment group and 1 patient (0.6%) in the placebo treatment group; none of the reactions were serious, were considered to be severe in intensity by the Investigator, or led to permanent treatment discontinuation. One of the 8 lixisenatide-treated patients had a TEAE adjudicated as an injection site reaction by the Allergic Reaction Assessment Committee (ARAC).

Eleven patients (8 patients [2.4%] and 3 patients [1.8%] in the lixisenatide and placebo treatment groups, respectively) had a TEAE adjudicated as an allergic reaction by the ARAC, 1 of which (toxic skin eruption in the placebo treatment group) was serious and was considered to be severe in intensity but recovered with corrective treatment despite continuation of study treatment. Three events from 3 patients were adjudicated as possibly related to investigational product (2 events of anaphylactic reaction in the lixisenatide treatment group and 1 event of angioedema in the placebo treatment group); these 3 events also led to permanent discontinuation of study treatment.

In total, 7 patients had events of changes in pancreatic enzymes, lipase, or amylase, or of pancreatitis reported on the eCRF AE form specific for "suspected pancreatitis" during the study: 6 patients (1.8%) in the lixisenatide treatment group and 1 patient (0.6%) in the placebo treatment group. Of these 7 patients, 1 patient in the lixisenatide treatment group had a confirmed diagnosis of pancreatitis reported during the study, approximately 9 months after the first dose of investigational product, which lasted for 38 days and led to permanent discontinuation of study treatment (during a gastroenterology evaluation, a computed tomography scan revealed dilatation of the pancreatic ducts, apparently due to chronic pancreatitis); approximately 11 weeks after the last dose of study medication, the patient had a second TEAE of pancreatitis (exacerbation of pancreatitis).

Four patients (1.2%) in the lixisenatide treatment group and 1 patient (0.6%) in the placebo treatment group had a TEAE of blood calcitonin increased (calcitonin levels ≥20 ng/L), only 1 of which had a calcitonin value ≥50 ng/L. None of the events were serious or considered to be severe in intensity by the Investigator; only 1 patient in each treatment group discontinued study treatment because of a TEAE of blood calcitonin increased.

A similar percentage of patients in each treatment group had a cardiac disorder TEAE (21 patients [6.4%] in the lixisenatide treatment group and 14 patients [8.4%] in the placebo treatment group); 17 of these patients (6 lixisenatide-treated patients [1.8%] and 11 placebo-treated patients [6.6%]) had a coronary artery disorder TEAE. For 1 patient in the lixisenatide treatment group, the coronary artery disorder TEAE (myocardial infarction) was serious and led to permanent discontinuation of study treatment and death.

There were no relevant changes in any of the laboratory tests. A small number of cases of elevated lipase or amylase (≥3 times upper limit of normal [ULN]) were observed (7 patients [2.2%] in the lixisenatide treatment group and 3 patients [1.9%] in the placebo treatment group had elevated lipase ≥3 ULN; 1 patient in the lixisenatide treatment group had elevated amylase ≥3 ULN). The overall incidence of calcitonin levels >ULN was low in the 2 treatment groups; 3 patients (1.1%) in the lixisenatide treatment group had a value of calcitonin ≥50 ng/L. For 2 of these 3 patients no TEAE was reported because the elevation was unconfirmed.

The vital signs data and the assessment of ECG readings did not reveal any specific safety concerns.

At baseline, 16 patients (6.0%) treated with lixisenatide and 8 patients (6.0%) treated with placebo were already antibody-positive. The percentage of patients who were antibody-positive in the lixisenatide treatment group increased with time, to a maximum at Week 76 of 141 patients (73.4%). After 100 weeks of lixisenatide-treatment, 28 patients (65.1%) were antibody-positive.

The antibody concentration was below the lower limit of quantification (LLOQ; 3.21 nmol/L) in more than half of the antibody-positive patients in the lixisenatide group at baseline and at Week 24; at other timepoints, the percentage of patients with an antibody concentration above the LLOQ was 50% or more. The median concentration of the anti-lixisenatide antibodies in plasma was 26.100 nmol/L at Week 2, 13.250 nmol/L at Week 4, 12.200 nmol/L at Week 24, 20.400 nmol/L at Week 76, and 16.800 nmol/L at Week 100.

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

***Pharmacokinetic results*:**

The median postinjection concentration of lixisenatide for anti-lixisenatide antibody-negative patients treated with 20 µg lixisenatide at the respective visit was 55.40 pg/mL, 60.50 pg/mL, 55.95 pg/mL, and 113.50 pg/mL at Weeks 2, 24, 76, and 100, respectively. The respective medians at predose were below the LLOQ at Weeks 2 and 24, 19.25 pg/mL at Week 76, and 43.15 pg/mL at Week 100.

In patients who were anti-lixisenatide antibody-positive and who were treated with 20 µg lixisenatide at the respective visit, the median postinjection concentration of lixisenatide increased with the duration of treatment: from 54.55 pg/mL at Week 2 to 426.50 pg/mL at Week 24, 632.00 pg/mL at Week 76, and 635.50 pg/mL at Week 100. The respective median at predose was below the LLOQ at Week 2 and increased to 218.00 pg/mL at Week 24, 646.50 pg/mL at Week 76, and 611.00 pg/mL at Week 100.

The biologically active concentration (predose) was above the LLOQ in 93 of 175 patients who were reported as antibody-positive at Week 24, with a median of 114.300 pg/mL. The median of the resulting active fraction (active lixisenatide/total lixisenatide) was 0.220.

Conclusions: [redacted]

Date of report: 08-Sep-2011