SYNOPSIS

Title of the study: A randomized, double-blind, placebo-controlled, parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of AVE0010 on top of metformin in patients with type 2 diabetes not adequately controlled with metformin (EFC6014)

Investigator(s): [redacted]

Study center(s): Multicenter (133 centers in 16 countries)

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 30/Jun/2008

Date last patient completed: 09/Mar/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 when it is used in the morning within 1 hour prior to the meal in comparison to placebo as an add-on treatment to metformin, in terms of glycosylated hemoglobin (HbA_{1c}) reduction (absolute change) over a period of 24 weeks in patients with type 2 diabetes.

Secondary:

To assess the effect of lixisenatide on glycemic control when administered in the evening within 1 hour prior to the meal in comparison to placebo in terms of HbA_{1c} reduction;
To assess the effects of lixisenatide on:

- Percentage of patients reaching HbA_{1c} <7% or HbA_{1c} ≤6.5%,
- Fasting plasma glucose (FPG),
- Plasma glucose, plasma insulin, C-peptide, glucagon, and proinsulin during a 2-hour standardized meal test (only in morning injection arms),
- Body weight,
- β-cell function assessed by homeostasis model assessment (HOMA)-β,
- Fasting plasma insulin (FPI),
- Adiponectin;

To assess lixisenatide safety and tolerability;
To assess lixisenatide pharmacokinetics (PK) using population PK approach;
To assess anti-lixisenatide antibody development;
To assess the effects of lixisenatide on β-cell function 4 weeks after investigational product discontinuation (only in patients from the morning injection arms in some selected centers).

Methodology: This was a randomized, double-blind, placebo-controlled, 4-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 regards to the treatments within the morning and evening injection administrations (ie, lixisenatide or placebo); however, the study drug volume (ie, dose of active drug or matching placebo) and the time of injection (morning versus evening) were not blinded.

Number of patients:	Planned:	680	Randomized:	680	Treated:	680
Evaluated:	Efficacy:	680	Safety:	680	Pharmacokinetics:	335

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus (T2DM) diagnosed at least 1 year before the screening visit; insufficiently controlled with metformin (at a stable dose of at least 1.5 g/day 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 [4-week ± 3 days follow-up was performed in patients from the morning injection arms]).

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 changes in 2-hour postprandial plasma glucose (PPG) and glucose excursion after a standardized meal from baseline to Week 24 (morning injection arms only), the percentage of patients requiring rescue therapy during the main 24-week double-blind treatment period, the change in FPI from baseline to Week 24, the change in adiponectin from baseline to Week 24, and the change in β-cell function assessed by HOMA-β from baseline to Week 24. During the standardized meal test (patients in the morning injection arms only), the changes in the following variables under fasting and 2-hour postprandial conditions were also assessed: plasma insulin (2-hour postprandial only), C-peptide, glucagon, proinsulin, and proinsulin-to-insulin ratio from baseline to Week 24. In addition (and only in patients from the morning injection arms who have completed the study treatment): the effect of lixisenatide on β-cell function evaluated 4 weeks after investigational product discontinuation by the change in HbA_{1c} from baseline and from end of treatment to 4 weeks after investigational product discontinuation, and by the change in glucose excursion, plasma glucose, plasma insulin, C-peptide, glucagon, proinsulin, and proinsulin-to-insulin ratio under fasting conditions and after a standardized meal, from baseline and from end of treatment to 4 weeks after investigational product discontinuation, and change in body weight from baseline and from the end of treatment to 4 weeks after investigational product discontinuation.

***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; and at the follow-up visit 4 weeks after investigational product discontinuation (applicable only in patients from morning arms who have completed the study treatment). The samples were taken in the morning, before the injection of the investigational product.

***Pharmacokinetics*:** Samples for assessment of plasma concentrations of lixisenatide were only taken in patients randomized to the morning injection arms at Weeks 2, 24, 76, and 100; samples were also taken before the start of rescue therapy and at the end of treatment, if the end of the 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.

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 patients in the morning placebo injection arm and in the evening placebo injection arm were combined together as 1 group in the analyses.

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 (morning injection placebo, evening injection placebo, morning injection lixisenatide, and evening injection lixisenatide), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%] and screening body mass index [BMI; <30 kg/m², ≥30 kg/m²]), 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. First, the morning injection arm was compared to the combined placebo arm (primary objective). If the test was statistically significant, the evening lixisenatide arm was compared to the combined placebo arm (secondary objective). 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. Efficacy variables assessed 4 weeks after the double-blind investigational product discontinuation (change from baseline to 4 weeks after investigational product discontinuation, and change from end of treatment to 4 weeks after investigational product discontinuation) were analyzed using a similar primary analysis ANCOVA model, with the corresponding covariate (ie, baseline or end of treatment values).

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 method stratified on randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%] and screening BMI [<30 kg/m², ≥30 kg/m²]). Results for all efficacy endpoints during the variable extension period and at the end of treatment were to be evaluated by descriptive statistics only, except for those analyses at 4 weeks after investigational product discontinuation.

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 antibody assessments: Data concerning anti-lixisenatide antibody status and concentration were listed and summarized using descriptive statistics (morning injection arm, evening injection arm, and combined).

Pharmacokinetics: Individual plasma concentrations and the biologically active concentration of lixisenatide were summarized using descriptive statistics (morning injection arm only).

Summary:

Efficacy results:

HbA_{1c}: The superiority of lixisenatide over placebo in terms of a reduction in HbA_{1c} control was demonstrated for both the morning injection lixisenatide group (primary objective) and the evening injection group (secondary objective), based on the predefined primary analysis of the least square (LS) mean changes from baseline to Week 24 in HbA_{1c} (LS mean change of -0.87% for the morning injection lixisenatide group, -0.75% for the evening injection lixisenatide group, and -0.38% for the combined placebo group). In comparison with placebo, the LS mean difference was -0.48% for the morning injection lixisenatide group ($p<0.0001$) and -0.37% for the evening injection lixisenatide group ($p<0.0001$).

At Week 24, the percentage of patients considered to be HbA_{1c} responders (ie, the percentage of patients with HbA_{1c} ≤6.5% or <7% at Week 24) was significantly higher in the morning injection lixisenatide group (23.8% and 43.0%, respectively; $p = 0.0003$ and $p<0.0001$, respectively, versus the combined placebo group) and in the evening injection lixisenatide group (19.2% and 40.6%, respectively; $p = 0.0120$ and $p<0.0001$, respectively, versus the combined placebo group) compared with the combined placebo group (10.4% and 22.0%, respectively).

PPG and glucose excursion: For 2-hour PPG after a standardized meal, the reduction from baseline to Week 24 was greater in the morning injection lixisenatide group compared with the morning injection placebo group (LS mean change: -5.92 mmol/L and -1.41 mmol/L, respectively). The LS mean difference for lixisenatide versus placebo was statistically significant (-4.51 mmol/L; 95% confidence interval [CI] -5.652, -3.371; $p<0.0001$). The reduction in glucose excursion after a standardized meal from baseline to Week 24 was greater in the morning injection lixisenatide group compared with the morning injection placebo group (LS mean change -4.64 mmol/L and -0.76 mmol/L, respectively). The LS mean difference for lixisenatide versus placebo was -3.88 mmol/L (95% CI: -4.818, -2.939).

FPG: For FPG, the reduction in the LS mean from baseline to Week 24 was -1.19 mmol/L for the morning injection lixisenatide group, -0.81 mmol/L for the evening injection lixisenatide group, and -0.25 mmol/L for the combined placebo group. The LS mean differences between the lixisenatide groups and the combined placebo group were statistically significant; for the morning injection lixisenatide group, -0.94 mmol/L (95% CI: -1.329, -0.559; $p<0.0001$) and for the evening injection lixisenatide group, -0.56 mmol/L (95% CI: -0.944, -0.173; $p = 0.0046$).

Body weight: For body weight, the reduction from baseline to Week 24 was similar in the morning and evening lixisenatide groups (LS mean change -2.01 and -2.02 kg, respectively); the LS mean change was -1.64 kg for the combined placebo group. The LS mean differences between the lixisenatide groups and the combined placebo group were not statistically significant: LS mean difference of -0.38 kg for the morning injection lixisenatide group (95% CI: -0.995, 0.239; $p = 0.2293$) and of -0.39 kg for the evening injection lixisenatide group (95% CI: -1.006, 0.230; $p = 0.2181$).

β-cell function: An increase in β-cell function, assessed by HOMA-β, was observed in both lixisenatide groups (LS mean change from baseline to Week 24 of 7.96 and 4.80 in the morning and evening injection lixisenatide groups, respectively), while a reduction in HOMA-β was seen in the combined placebo group (LS mean change of -4.16). The LS mean differences between the lixisenatide groups and the combined placebo group were 12.12 (95% CI: 5.685, 18.559) for the morning injection lixisenatide group and 8.96 (95% CI: 2.450, 15.477) for the evening injection lixisenatide group.

Rescue therapy: Lower percentages of patients required rescue therapy in both lixisenatide-treated groups during the main 24-week double-blind treatment period (2.7% for morning injection and 3.9% for evening injection) compared with the combined placebo group (10.6%). During the variable extension period, the percentage of patients requiring rescue therapy increased in both treatment groups, but was still lower in both lixisenatide groups compared with placebo. During the whole study, 23.1%, 20.8%, and 32.9% of patients in the morning and evening injection lixisenatide groups, and in the combined placebo group, respectively, required rescue therapy.

Fasting plasma insulin: The reduction in FPI from baseline to Week 24 was similar in the morning injection lixisenatide group (LS mean change -5.09 pmol/L) and the combined placebo group (LS mean change -6.23 pmol/L). In the evening injection lixisenatide group, the LS mean change was -1.88 pmol/L. The LS mean difference between the lixisenatide groups and the combined placebo group was not statistically significant for FPI (LS mean difference of 1.14 pmol/L [95% CI: -6.275, 8.561] for the morning injection lixisenatide group and of 4.35 pmol/L [95% CI: -3.121, 11.826] for the evening injection lixisenatide group).

Adiponectin levels: The increase in adiponectin from baseline to Week 24 was similar in all 3 groups (LS mean change 0.55 μg/mL, 0.58 μg/mL, and 0.54 μg/mL in the morning injection lixisenatide group, evening injection lixisenatide group, and combined placebo group, respectively).

Meal-related glucagon, insulin, proinsulin, and C-peptide: Decreases from baseline to Week 24 were observed in both the lixisenatide and placebo morning injection groups for fasting and 2-hour postprandial glucagon, 2-hour postprandial plasma insulin, fasting and 2-hour postprandial proinsulin, and fasting and 2-hour postprandial C-peptide. Greater decreases were observed in the lixisenatide morning injection group for 2-hour postprandial glucagon and proinsulin, compared with the placebo morning injection group. The change was minimal for both fasting and 2-hour postprandial proinsulin-to-insulin ratio in both the lixisenatide and placebo morning injection groups.

Extension period: The clinically beneficial effects on the efficacy variables (HbA_{1c}, 2-hour PPG, glucose excursion, FPG, and HOMA-β) observed during the main 24-week treatment period were maintained during the variable extension period. At the end of the 4-week follow-up period there were no differences in efficacy parameters between the placebo and lixisenatide morning injection groups.

Safety results:

Overview of TEAEs: The proportion of patients who experienced TEAEs was comparable across the lixisenatide-treated groups (84.7% in the morning injection lixisenatide group and 83.5% in the evening injection lixisenatide group), and higher in these groups than in the combined placebo group (75.3%). One patient in the morning injection lixisenatide group had a TEAE leading to death. Two patients in the evening injection lixisenatide group died due to posttreatment AEs. Fifty-eight patients had serious TEAEs during the whole study (8.2% in the morning injection lixisenatide group, 10.2% in the evening injection lixisenatide group, and 6.5% in the combined placebo group). The percentage of patients with TEAEs leading to treatment discontinuation was similar in the lixisenatide-treated groups (8.2% for the morning injection group and 9.4% for the evening injection group), and higher in the lixisenatide groups than in the combined placebo group (3.5%). The most common TEAE leading to treatment discontinuation was nausea in both lixisenatide-treated groups (6 patients [2.4%] in the morning injection lixisenatide group and 7 patients [2.7%] in the evening injection lixisenatide group). No patients discontinued treatment because of nausea in the combined placebo group.

Common TEAEs: The most commonly reported TEAE for lixisenatide-treated patients was nausea (64 patients [25.1%] in the morning injection lixisenatide group and 63 patients [24.7%] in the evening injection lixisenatide group, compared with 16 patients [9.4%] in the combined placebo group), followed by vomiting (35 patients [13.7%] in the morning injection lixisenatide group and 40 patients [15.7%] in the evening injection lixisenatide group, compared with 9 placebo-treated [5.3%] patients). This is consistent with the known safety profile of glucagon-like peptide 1(GLP-1) receptor agonists. Few patients treated with lixisenatide discontinued study treatment because of nausea (6 patients [2.4%] in the morning injection lixisenatide group, 7 patients [2.7%] in the evening injection lixisenatide group, and no patients in the combined placebo group) or vomiting (2 patients [0.8%] in the morning injection lixisenatide group, 5 patients [2.0%] in the evening injection lixisenatide group, and no patients in the combined placebo group).

Hypoglycemia events: Symptomatic hypoglycemia events, per protocol definition, were reported, during the whole study for 18 patients (7.1%) in the morning injection lixisenatide group, 22 patients (8.6%) in the evening injection lixisenatide group, and 4 patients (2.4%) in the combined placebo group. No events of severe symptomatic hypoglycemia per protocol definition were reported in the study. One patient (0.4%) in the morning injection lixisenatide group and 3 patients (1.2%) in the evening injection lixisenatide group permanently discontinued study treatment due to a TEAE of symptomatic hypoglycemia.

Injection site reactions: Injection site reactions were reported for 17 patients (6.7%) in the morning injection lixisenatide group, 17 patients (6.7%) in the evening injection lixisenatide group, and 6 patients (3.5%) in the combined placebo group. None of the reactions were serious or were considered to be severe in intensity by the Investigator.

Allergic reactions: TEAEs that were adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee (ARAC) were reported for 10 patients (3 patients [1.2%] in the morning injection lixisenatide group, 4 patients [1.6%] in the evening injection lixisenatide group, and 3 patients [1.8%] in the combined placebo group). Three events in 2 patients (1 patient in the morning injection lixisenatide group with serious events of maculo-papular rash and angioedema [adjudicated by the ARAC as anaphylactic reaction and angioedema, respectively] and 1 patient in the evening injection lixisenatide group with nonserious allergic dermatitis [adjudicated by the ARAC as urticaria (hives)]) were adjudicated as allergic reactions, possibly related to investigational product by the ARAC. The 3 events led to permanent treatment discontinuation in both patients. Two additional patients had nonserious allergic TEAEs that led to permanent discontinuation of study treatment but the events were not adjudicated as allergic reactions by the ARAC: 1 patient in the morning injection lixisenatide group with rosacea and 1 patient in the evening injection lixisenatide group with dermatitis allergic.

Pancreatic enzymes: In total, 13 patients had events of changes in pancreatic enzymes, lipase, or amylase reported on the specific AE case report form (CRF) for suspected pancreatitis during the study: 3 patients (1.2%) in the morning injection lixisenatide group, 9 patients (3.5%) in the evening injection lixisenatide group, and 1 patient (0.6%) in the combined placebo group. There were no confirmed cases of pancreatitis according to the local gastroenterologist and/or local imaging assessments. One event was serious (increased pancreatic enzymes, in the evening injection lixisenatide group) and led to permanent treatment discontinuation. Additionally, 1 patient with suspected pancreatitis, 1 patient with blood amylase and lipase increased (both in the evening injection lixisenatide group), and 1 patient with lipase increased in the morning injection lixisenatide group permanently discontinued treatment.

Calcitonin: TEAEs of blood calcitonin increased (calcitonin levels ≥20 ng/L) were reported for 11 patients (4 patients [1.6%] in each lixisenatide-treated group and 3 patients [1.8%] in the combined placebo group), of which 1 in the morning injection lixisenatide group and 2 in the evening injection lixisenatide group led to treatment discontinuation in 3 patients.

Cardiac disorders: Cardiac disorders were reported for 17 patients (6.7%) in the morning injection lixisenatide group, 21 patients (8.2%) in the evening injection lixisenatide group, and 5 patients (2.9%) in the combined placebo group.

Hematology and clinical chemistry: The overall incidence rate of potentially clinically significant abnormalities for hematology, lipid parameters, pancreatic enzymes, creatinine, uric acid, and liver function tests was generally similar in all treatment groups.

Eleven patients (2.2%) in the combined lixisenatide group and 4 patients (2.4%) in the combined placebo group had elevated lipase (≥3 upper limit of normal [ULN]). Four patients (0.8%) in the combined lixisenatide group and 1 patient (0.6%) in the combined placebo group had elevated amylase ≥3 ULN. Three patients had a calcitonin level of ≥50 ng/L (1 patient in the morning injection lixisenatide group and 2 patients in the evening injection lixisenatide group).

Vital signs and ECG: The vital signs data and the assessment of ECG readings did not reveal any specific safety signal. Small changes in systolic blood pressure, diastolic blood pressure, and heart rate were observed in all treatment groups from baseline to the last treatment value.

Anti-lixisenatide antibody assessments: Anti-lixisenatide antibody data will be reported in an amended version of this CSR.

Pharmacokinetic results:

PK data will be reported in amended version of this CSR.

Conclusions: [redacted]

Date of report: 23-Aug-2011