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 extensionpatient assessing the efficacy and safety of AVE0010 on top of pioglitazone in patients with type 2 diabetes not adequately controlled with pioglitazone (EFC6017)

Investigator(s): [redacted]

Study center(s): Multicenter (150 centers in 13 countries)

Publications (reference): Not applicable.

Study period:

Date first patient enrolled: 29/Sep/2008

Date last patient completed: 29/Jun/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 pioglitazone in type 2 diabetes patients treated with pioglitazone in terms of absolute glycosylated hemoglobin (HbA_{1c}) reduction over a period of 24 weeks.

Secondary:

To assess the effects of lixisenatide on:

- Percentage of patients reaching HbA_{1c} <7%,
- Percentage of patients reaching HbA_{1c} ≤6.5%,
- Fasting plasma glucose (FPG),
- Body weight,
- β-cell function assessed by homeostatic model assessment of β-cell function (HOMA-β),
- Fasting plasma insulin (FPI);

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:	484	Treated:	484
Evaluated:	Efficacy:	479	Safety:	484	PK:	477

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus (T2DM) diagnosed at least 1 year before the screening visit; insufficiently controlled with pioglitazone at a stable dose of 30 mg/day for at least 3 months prior to screening; HbA_{1c} ≥7% and ≤10% at screening; and, for patients treated with metformin, metformin treatment at a stable dose of 1.5 g/day for at least 3 months prior to 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 FPG, body weight, β-cell function (assessed by HOMA-β), and in FPI 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. 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 FPG from baseline to Week 24; change in body weight from baseline to Week 24; 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 double-blind treatment period; and the change in FPI from baseline to Week 24). 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 double-blind treatment period) were analyzed using a Cochran-Mantel-Haenszel 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 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 -0.90% and -0.34% in the lixisenatide and placebo treatment groups, respectively). The LS mean difference for lixisenatide versus placebo was -0.56% ($p<0.0001$). 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 (89 patients [28.9%] for HbA_{1c} ≤6.5% and 161 patients [52.3%] for HbA_{1c} <7%) versus the placebo treatment group (15 patients [10.1%] for HbA_{1c} ≤6.5% and 39 patients [26.4%] for HbA_{1c} <7%) ($p<0.0001$ for both HbA_{1c} ≤6.5% and HbA_{1c} <7%). The reduction in HbA_{1c} was similar in anti-lixisenatide antibody-positive and anti-lixisenatide antibody-negative patients, and there was no influence of the antibody concentration on the change in HbA_{1c}, thus indicating no impact of anti-lixisenatide antibodies on the change in HbA_{1c}.

For FPG, the LS mean change from baseline to Week 24 was greater in the lixisenatide treatment group compared with the placebo treatment group (-1.16 mmol/L and -0.32 mmol/L in the lixisenatide and placebo treatment groups, respectively); the LS mean difference between the 2 treatment groups (-0.84 mmol/L) was statistically significant (95% confidence interval [CI]: -1.209, -0.467; $p<0.0001$).

For body weight, an LS mean decrease from baseline to Week 24 was observed in the lixisenatide treatment group compared with an LS mean increase in the placebo treatment group (-0.21 kg and 0.21 kg in the lixisenatide and placebo treatment groups, respectively); the treatment difference was not statistically significant (-0.41 kg; 95% CI: -1.031, 0.201; $p = 0.1864$).

The LS mean change in HOMA-β from baseline to Week 24 was similar for the 2 treatment groups (6.72 and 6.98 in the lixisenatide and placebo treatment groups, respectively); the LS mean difference versus placebo was -0.25 (95% CI: -6.579, 6.070).

The percentage of patients requiring rescue therapy during the main 24-week treatment period was 3-fold lower in the lixisenatide treatment group (12 patients [3.8%]) compared with the placebo treatment group (18 patients [11.3%]) ($p = 0.0011$).

The LS mean decrease in FPI from baseline to Week 24 was greater in the lixisenatide treatment group compared with the placebo treatment group (-10.36 pmol/L and -1.01 pmol/L in the lixisenatide and placebo treatment groups, respectively); the LS mean difference between the 2 treatment groups was -9.36 pmol/L (95% CI: -16.586, -2.124).

The beneficial effects on the efficacy variables (HbA_{1c}, FPG, HOMA-β, and FPI) observed during the main 24-week treatment period were maintained during the variable extension period. A steady increase in body weight from baseline was observed in both treatment groups during the variable extension period. The percentage of patients requiring rescue therapy over the whole double-blind treatment period was lower in the lixisenatide treatment group (21.6%) than in the placebo treatment group (36.5%).

Safety results:

An overview of the safety results observed during the whole study is provided in the following table. One patient (in the placebo treatment group) had a TEAE leading to death (acute myocardial infarction). Forty patients had serious TEAEs (7.7% and 9.3% in the lixisenatide and placebo treatment groups, respectively). The percentage of patients with TEAEs leading to permanent treatment discontinuation was similar in the 2 treatment groups (9.3% and 7.5% in the lixisenatide and placebo treatment groups, respectively). The most common TEAE leading to permanent treatment discontinuation was nausea in the lixisenatide treatment group (6 patients [1.9%] 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=161)	**Lixisenatide (N=323)**
Patients with any TEAE	134 (83.2%)	284 (87.9%)
Patients with any serious TEAE	15 (9.3%)	25 (7.7%)
Patients with any TEAE leading to death	1 (0.6%)	0
Patients with any TEAE leading to permanent treatment discontinuation	12 (7.5%)	30 (9.3%)

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

The proportion of patients who experienced TEAEs was 87.9% and 83.2% in the lixisenatide and placebo treatment groups, respectively. During the on-treatment period for the whole study, the most commonly reported TEAE in the lixisenatide treatment group was nausea (84 patients [26.0%] in the lixisenatide treatment groups and 22 patients [13.7%] in the placebo treatment group), which is consistent with the known safety profile of glucagon-like peptide 1 receptor agonists. The second most frequently reported TEAE in the lixisenatide treatment group was nasopharyngitis (53 patients [16.4%] in the lixisenatide treatment group and 24 patients [14.9%] in the placebo treatment group), which was the most commonly reported TEAE in the placebo treatment group. The percentage of patients who had TEAEs during the main 24-week treatment period was similar in the 2 treatment groups (72.4% and 72.7% in the lixisenatide and placebo treatment groups, respectively).

The percentage of patients who had symptomatic hypoglycemia fulfilling the protocol definition during the study was 23 patients (7.1%) in the lixisenatide treatment group and 7 patients (4.3%) in the placebo treatment group. The number of symptomatic hypoglycemia events per 100 patient years was 8.9 in the lixisenatide treatment group compared with 3.1 in the placebo treatment group. No events of severe symptomatic hypoglycemia were reported during the study. No hypoglycemia-related TEAEs led to permanent discontinuation of study treatment and none of the hypoglycemia-related TEAEs were serious.

Injection site reactions were reported for 22 patients (6.8%) in the lixisenatide treatment group and 8 patients (5.0%) 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.

Twelve patients (9 patients [2.8%] and 3 patients [1.9%] in the lixisenatide and placebo treatment groups, respectively) had a TEAE adjudicated as an allergic reaction by the ARAC. Five events from 3 patients (0.9%) in the lixisenatide treatment group were adjudicated as possibly related to investigational product (1 patient with dermatitis allergic, 1 patient with urticaria, and 1 patient with angioedema, anaphylactic reaction, and conjunctivitis allergic); none of the patients in the placebo treatment group had an allergic reaction adjudicated as possibly related to investigational product. The 3 patients with events adjudicated as possibly related to the investigational product permanently discontinued study treatment due to these events; the possibly related events leading to discontinuation were dermatitis allergic, urticaria, and anaphylactic reaction.

In total, 4 patients had events of increases in lipase or amylase reported on the electronic case report form AE form specific for "suspected pancreatitis" during the study: 2 patients (0.6%) in the lixisenatide treatment group and 2 patients (1.2%) in the placebo treatment group. No confirmed diagnoses of pancreatitis were reported during the study in either treatment group. None of the events were considered to be severe in intensity and none were serious. One placebo-treated patient discontinued study treatment due to events of both lipase increased and blood amylase increased.

A similar percentage of patients in each treatment group had a TEAE of blood calcitonin increased (calcitonin levels ≥20 ng/L) (9 patients [2.8%] in the lixisenatide treatment group and 4 patients [2.5%] in the placebo treatment group); 1 patient in each treatment group had a TEAE of blood calcitonin increased and a calcitonin value ≥50 ng/L. One of the events was serious; none were considered to be severe in intensity by the Investigator. Three patients (1 patient [0.3%] and 2 patients [1.2%] in the lixisenatide and placebo treatment groups, respectively) permanently discontinued study treatment because of a TEAE of blood calcitonin increased.

The percentage of patients with a TEAE in the cardiac disorders system organ class was the same in both treatment groups (22 patients [6.8%] in the lixisenatide treatment group and 11 patients [6.8%] in the placebo treatment group). Seven patients (2.2%) in the lixisenatide treatment group and 3 patients (1.9%) in the placebo treatment group had a coronary artery disorder TEAE. One patient in the placebo treatment group had a coronary artery disorder TEAE (acute myocardial infarction), which was serious and led to death; this event was not considered to be related to study treatment by the Investigator. An additional 5 patients (3 patients [0.9%] in the lixisenatide treatment group and 2 patients [1.2%] in the placebo treatment group) had serious coronary artery disorder TEAEs. One patient in each treatment group (0.3% and 0.6% in the lixisenatide and placebo treatment groups, respectively) had a coronary artery disorder TEAE that led to permanent discontinuation of study treatment.

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

At baseline, 8 patients (3.3%) treated with lixisenatide and 3 patients (2.3%) treated with placebo were already anti-lixisenatide antibody-positive. The percentage of anti-lixisenatide antibody-positive patients in the lixisenatide treatment group increased with time and was 77.2% at Week 100.

Overall, 78/208 (37.5%) of the patients in the lixisenatide treatment group were negative for anti-lixisenatide antibodies at Week 24. Of the 140 anti-lixisenatide antibody-positive patients who had an assessment of the antibody concentration at Week 24, 83 patients (59.3%) had an antibody concentration below the LLOQ. At Week 76, 56/205 patients (27.3%) were anti-lixisenatide antibody-negative. Of the 166 anti-lixisenatide antibody-positive patients who had an assessment of antibody concentration at Week 76, 94 patients (56.6%) had an antibody concentration <LLOQ.

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

Pharmacokinetic results:

In patients who were anti-lixisenatide antibody-negative and who were treated with 20 µg lixisenatide per day, the median postinjection total plasma concentrations of lixisenatide were 56.00 pg/mL, 67.50 pg/mL, 107.00 pg/mL, and 56.40 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 31.30 pg/mL at Week 100.

In patients who were anti-lixisenatide antibody-positive and who were treated with 20 µg lixisenatide per day, the median postinjection total plasma concentrations of lixisenatide increased with the duration of treatment: from 70.30 pg/mL at Week 2, to 561.00 pg/mL at Week 24, 644.00 pg/mL at Week 76, and 764.00 pg/mL at Week 100. The respective median at predose was below the LLOQ at Week 2 and increased to 375.50 pg/mL at Week 24, 482.00 pg/mL at Week 76, and 638.00 pg/mL at Week 100.

The biologically active concentration (predose) was above the LLOQ in 74 of 128 patients who were reported as anti-lixisenatide antibody-positive at Week 24, with a median of 115.85 pg/mL. The median of the resulting active fraction (active lixisenatide concentration/total lixisenatide concentration) was 0.178 for these patients.

Conclusions: [redacted]

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