SYNOPSIS

Title of the study:	A randomized, open-label, active-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of AVE0010 versus exenatide on top of metformin in patients with type 2 diabetes not adequately controlled with metformin (EFC6019)
Investigator(s):	[redacted]
Study center(s):	Multicenter (122 centers in 18 countries)
Publications (reference):	Not applicable
Study period:	
Date first patient enrolled:	23-Jun-2008
Date last patient completed:	18-Nov-2010
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 exenatide (Byetta®) 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 effects of lixisenatide, in comparison to exenatide, on:
  - Percentage of patients reaching HbA_{1c} <7% or HbA_{1c} ≤6.5%,
  - Fasting plasma glucose (FPG),
  - Body weight;
- To assess lixisenatide safety and tolerability;
- To assess the impact of gastrointestinal tolerance on quality of life (QoL) (patient assessment of upper gastrointestinal disorders – quality of life [PAGI-QOL]).

Methodology: This was a randomized, open-label, active-controlled, 2-arm, balanced design, parallel group study with 2-step titration regimen for lixisenatide (10 µg once daily [QD] for 1 week, then 15 µg QD for 1 week, followed by the maintenance dose of 20 µg QD). A 1-step titration regimen was used for the active comparator, exenatide (5 µg twice daily [BID] for 4 weeks, followed by the maintenance dose of 10 µg BID).

Number of patients:	Planned:	600	Randomized:	639	Treated:	639
Evaluated:	Efficacy:	630	Safety:	634		

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus (T2DM) diagnosed at least 1 year before the screening visit; receiving metformin treatment 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 open-label treatment; variable open-label extension)

Duration of observation: Approximate minimum duration of 78 weeks (up to 2 weeks screening + 24 weeks main open-label treatment + variable extension + 3 days follow-up)

Reference therapy: exenatide

Dose: 5 µg and 10 µg

Administration: subcutaneous injection

Batch number(s): 5 µg: [redacted]; 10 µg: [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 and body weight 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.

QoL was assessed using the following criterion: the change in the perceived impact of gastrointestinal disorders on health-related QoL (PAGI-QOL) from baseline to Week 24.

Statistical methods:

Efficacy: The efficacy of lixisenatide was assessed using the modified intent-to-treat population (mITT), which consisted of all patients who were randomized (analyzed "as randomized"), received at least 1 dose of open-label 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 exenatide), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%], screening body mass index; <30, ≥30 kg/m²]), and country as fixed effects and using the baseline HbA_{1c} as a covariate. Noninferiority was demonstrated if the upper bound of the 2-sided 95% confidence interval (CI) of the difference in the adjusted mean change in HbA_{1c} from baseline to Week 24 between lixisenatide and exenatide in the mITT population was ≤0.4%. If noninferiority was established, a corresponding check of statistical superiority was performed.

No formal statistical test was performed for any of the secondary efficacy endpoints. 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% 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 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.

QoL data were also analyzed using the previously described ANCOVA model and descriptive statistics were provided.

Summary:

Efficacy results:

Noninferiority of lixisenatide versus exenatide was demonstrated based on the predefined primary analysis of the least square (LS) mean changes from baseline to Week 24 in HbA_{1c} (-0.79% and -0.96% in the lixisenatide and exenatide treatment groups, respectively), using a noninferiority margin of 0.4% HbA_{1c} (LS mean difference versus exenatide was 0.17%; 95% CI: 0.033, 0.297). Superiority of lixisenatide over exenatide was not demonstrated. At Week 24, the percentage of patients considered to be responders, with HbA_{1c} <7%, was similar in the lixisenatide and exenatide treatment groups (48.5% and 49.8%, respectively); the percentage of patients considered to be responders, with HbA_{1c} ≤6.5%, was lower in the lixisenatide treatment group (28.5%) compared with the exenatide treatment group (35.4%).

For FPG, the LS mean change from baseline to Week 24 was -1.22 mmol/L for the lixisenatide treatment group and -1.45 mmol/L for the exenatide treatment group (LS mean difference versus exenatide was 0.23 mmol/L).

There was a baseline imbalance in mean body weight between the 2 treatment groups (94.51 kg in the lixisenatide treatment group and 96.69 kg in the exenatide treatment group [mITT population]). The LS mean body weight loss from baseline at Week 24 was 2.96 kg for the lixisenatide-treated patients and 3.98 kg for the exenatide-treated patients (LS mean difference versus exenatide was 1.02 kg). About 25.1% lixisenatide-treated patients and 31.4% exenatide-treated patients had ≥5% weight loss from baseline to Week 24.

The percentage of patients requiring rescue therapy during the main 24-week treatment period was small and similar in the 2 treatment groups (2.2% and 3.8% in the lixisenatide and exenatide treatment groups, respectively).

The beneficial effects on the efficacy variables (HbA_{1c}, FPG, and body weight) observed during the main 24-week treatment period were maintained during the variable extension period. The percentage of patients requiring rescue therapy increased at a similar rate in the lixisenatide and exenatide treatment groups during the variable extension period.

Safety results:

An overview of the safety results observed during the whole study is provided in the following table. Six patients (3 patients in each treatment group) had TEAEs leading to death. Forty-eight patients had serious TEAEs, with a similar incidence rate in each treatment group (8.2% and 7.0% in the lixisenatide and exenatide treatment groups, respectively). The percentage of patients with TEAEs leading to permanent treatment discontinuation was the same in both groups (14.2%). The most common TEAE leading to permanent treatment discontinuation was nausea in both treatment groups (15 patients [4.7%] in the lixisenatide group and 19 patients [6.0%] in the exenatide group). Similar results were seen for the 24-week treatment period.

	Lixisenatide (N=318)	**Exenatide (N=316)**
Patients with any TEAE	257 (80.8%)	264 (83.5%)
Patients with any serious TEAE	26 (8.2%)	22 (7.0%)
Patients with any TEAE leading to death	3 (0.9%)	3 (0.9%)
Patients with any TEAE leading to permanent treatment discontinuation	45 (14.2%)	45 (14.2%)

TEAE: Treatment Emergent Adverse Event
n (%) = number and percentage of patients with at least one adverse event

The proportion of patients who experienced TEAEs was generally comparable between the lixisenatide-treated and exenatide-treated groups (80.8% and 83.5%, respectively). The most commonly reported TEAE was nausea in both treatment groups, which is consistent with the known safety profile of glucagon-like peptide 1 receptor agonists. A lower percentage of patients had nausea in the lixisenatide treatment group (91 patients [28.6%]) compared with exenatide treatment group (119 patients [37.7%]).

In total, 62 patients had symptomatic hypoglycemia fulfilling the protocol definition during the study; there was a lower frequency of symptomatic hypoglycemia in the lixisenatide treatment group (16 patients [5.0%]) compared with the exenatide treatment group (46 patients [14.6%]). In addition, fewer hypoglycemic events were reported for patients in the lixisenatide group (39 events) compared with patients in the exenatide group (93 events); the number of events per 100 patient years was 9 in the lixisenatide group compared with 22.1 in the exenatide group. Similar results were seen for patients who had blood glucose levels <60 mg/dL (15 patients [4.7%] and 38 patients [12.0%] in the lixisenatide and exenatide treatment groups, respectively); the number of events per 100 patient years was 7.9 in the lixisenatide group compared with 18.3 in the exenatide group. No events of severe symptomatic hypoglycemia were reported during the study.

Injection site reactions were reported for 29 patients (9.1%) in the lixisenatide treatment group and by 7 patients (2.2%) in the exenatide treatment group, none of which were serious or were considered to be severe by the Investigator; 3 of the patients (0.9%) in the lixisenatide group permanently discontinued study treatment due to an event of injection site reaction. It should be noted that the volume of injection was 5 times greater in the lixisenatide group (0.2 mL) than in the exenatide group (0.04 mL).

Nine patients (6 patients [1.9%] and 3 patients [0.9%] in the lixisenatide and exenatide treatment groups, respectively) had a TEAE adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee (ARAC), 1 of which (urticaria in the lixisenatide treatment group) was serious but recovered with corrective treatment despite continuation of study treatment; none of the events were considered to be severe by the Investigator. None of the TEAEs adjudicated as an allergic reaction were considered to be related to investigational product by ARAC.

There were no relevant changes in any of the laboratory tests. A small number of cases of elevated lipase or amylase (≥3 x upper limit of normal [ULN]) were observed (11 patients in each treatment group had elevated lipase ≥3 ULN; 3 patients in the lixisenatide treatment group had elevated amylase ≥3 ULN). No confirmed diagnoses of pancreatitis were reported during the study in the lixisenatide treatment group. The overall incidence of calcitonin levels >ULN was low and similar in the 2 treatment groups; none of the patients had a calcitonin level ≥50 ng/L.

Slight decreases in systolic and diastolic blood pressure were observed in both treatment groups. There were no clinically relevant changes in heart rate or ECG parameters.

The mean change from baseline to Week 24 in PAGI-QOL was similar in the 2 groups: -0.11 in the lixisenatide treatment group and -0.06 in the exenatide treatment group (LS mean difference versus exenatide was -0.03).

Conclusions:

[redacted]

Date of report: 13-Jan-2015