SYNOPSIS

Title of the study: A randomized, double-blind, placebo-controlled, parallel-group, multicenter 12-week study assessing the efficacy and safety of AVE0010 in patients with type 2 diabetes not treated with antidiabetic agents

Investigator(s): [redacted]

Study center(s): Multicenter (68 centers in 12 countries)

Publications (reference): Monotherapy with GLP-1 receptor agonist, lixisenatide, significantly improves glycemic control in type 2 diabetic patients. Diabetologia. 2010;53, (Supp 1): S330

Study period:

Date first patient enrolled: 14/May/2008

Date last patient completed: 14/Dec/2009

Phase of development: 3

Objectives:

Primary: To assess the effects of AVE0010 (hereinafter referred to by the international nonproprietary name, lixisenatide) on glycemic control using a 2-step dose titration regimen in comparison to placebo in terms of glycosylated hemoglobin (HbA_{1c}) reduction over a period of 12 weeks in patients with type 2 diabetes.

Secondary:

- To assess the effects of lixisenatide on:
  - Glycemic control in comparison to placebo in terms of HbA_{1c} reduction when it is used in a 1-step dose titration regimen over a period of 12 weeks,
  - Body weight at Week 12,
  - Fasting plasma glucose at Week 12,
  - 2-hour postprandial plasma glucose (PPG) after a standardized meal at Week 12 (in a substudy of all patients in selected centers),
- To assess lixisenatide safety and tolerability,
- To assess lixisenatide pharmacokinetics (PK) using population PK approach,
- To assess anti-lixisenatide antibody development.

Methodology: This was a double-blind, randomized, 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) or a 1-step titration regimen (10 µg QD for 2 weeks followed by the maintenance dose of 20 µg QD). The study was double-blind with regard to active and placebo treatments; however neither the study drug volume nor the titration regimens (ie, 2-step or 1-step) were blinded.

Number of patients:	Planned:	360	Randomized:	361	Treated:	361
Evaluated:	Efficacy:	359	Safety:	361	Pharmacokinetics:	356

Diagnosis and criteria for inclusion: Patients with type 2 diabetes diagnosed for at least 2 months at the time of the screening visit; not treated by an antidiabetic pharmacological agent in the 3 months preceding screening; and HbA_{1c} ≥7% and ≤10% at screening.

Investigational product: lixisenatide

Dose: 10 µg / 15 µg / 20 µg

Administration: subcutaneous injection

Batch number(s): [redacted]

Duration of treatment: 12 weeks

Duration of observation: 15 weeks ±10 days

Reference therapy: placebo

Dose: 10 µg / 15 µg / 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 12, the percentage of patients with HbA_{1c} <7% or ≤6.5% at Week 12, the changes in body weight, 2-hour PPG (after a standardized meal), and fasting plasma glucose between Baseline and Week 12; and the percentage of patients requiring rescue therapy during the double-blind treatment 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, and 12. The samples were taken in the morning (pre-injection of the investigational product).

Pharmacokinetics: Samples for assessment of plasma concentrations of lixisenatide were taken on Weeks 2, 4, and 12. Samples were taken once prior to injection of the investigational product and then once within 1 to 4 hours post-injection. In vitro active concentration of lixisenatide was also determined.

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 change in HbA_{1c} from Baseline to Week 12) was analyzed using an analysis of covariance (ANCOVA) model with treatment groups (2-step lixisenatide titration and placebo arms, 1-step lixisenatide titration and placebo arms), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%] and screening BMI [<30, ≥30 kg/m^2]) and country as fixed effects, and using the baseline HbA_{1c} value as a covariate.

A stepwise testing procedure was applied in order to ensure control of type 1 error. First, 2-step lixisenatide titration regimen was compared with the combined placebo group. If the test was statistically significant then the 1-step lixisenatide titration regimen was compared with the combined placebo group. Similar to the approach used for the primary endpoint, data for all continuous secondary efficacy variables were analyzed using the above described ANCOVA model with a corresponding covariate. Data for the categorical secondary efficacy variables (ie, % of patients with HbA_{1c} <7.0% or % of patients with HbA_{1c} ≤6.5% (HbA_{1c} responders), and % of patients requiring rescue therapy at Week 12) were analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata (screening HbA_{1c} <8.0, ≥8.0% and screening BMI <30, ≥30 kg/m^2).

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, laboratory, vital signs, and ECG data was descriptive.

Anti-lixisenatide antibodies: Data concerning anti-lixisenatide antibody status and concentration were listed and summarized using descriptive statistics.

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

Summary:

Efficacy results:

Treatment with lixisenatide resulted in a statistically significant decrease in HbA_{1c} from Baseline to Week 12. The least square (LS) mean changes from Baseline to endpoint in HbA_{1c} were -0.19% for the combined placebo group, -0.73% for the lixisenatide 2-step titration arm (LS mean difference versus placebo = -0.54%; p-value = <.0001), and -0.85% for the lixisenatide 1-step titration arm (LS mean difference versus placebo = -0.66%; p-value = <.0001). The analysis of HbA_{1c} responders (ie, patients with HbA_{1c} ≤6.5 or <7% at endpoint) using the CMH method also showed a significant treatment difference versus placebo for both lixisenatide-treated groups.

Treatment with lixisenatide also improved post-prandial glycemic control as shown by the results for the 2-hour post-prandial plasma glucose assessment and for glucose excursion. A statistically significant improvement in PPG was demonstrated in each of the lixisenatide-treated arms, compared with the combined placebo group.

There was a mean decrease in body weight of approximately 2 kg in each of the treatment groups, with no significant difference observed between groups.

Treatment with lixisenatide demonstrated a clinically relevant improvement in fasting plasma glucose compared with the combined placebo group.

The percentage of patients requiring rescue therapy was similar across treatment groups (1.7% in the 2-step titration arm, 0.8% in the 1-step titration arm, and 2.5% in the combined placebo group).

Safety results:

An overview of the safety results observed in the study is provided in the following table. There were no deaths reported during the study. There were 6 SAEs during the study, 5 in patients treated with placebo and 1 in a patient treated with lixisenatide (2-step titration arm). Nine (9) patients discontinued the study due to TEAEs, 1 (0.8%) treated with placebo, 8 treated with lixisenatide (5 [4.2%] in the 2-step titration arm, and 3 [2.5%] in the 1-step titration arm). The main reason for treatment discontinuation in the lixisenatide-treated groups was the occurrence of adverse events from the gastrointestinal disorders system organ class.

	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Patients with any TEAE	25 (41.0%)	30 (49.2%)	55 (45.1%)	63 (52.5%)	65 (54.6%)	128 (53.6%)
Patients with any serious TEAE	3 (4.9%)	2 (3.3%)	5 (4.1%)	1 (0.8%)	0	1 (0.4%)
Patients with any TEAE leading to death	0	0	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	1 (1.6%)	0	1 (0.8%)	5 (4.2%)	3 (2.5%)	8 (3.3%)

TEAE: Treatment Emergent Adverse Event.

n (%) = number and percentage of patients with at least one adverse event

The incidence of TEAEs was slightly higher in all lixisenatide treatment groups compared to the placebo groups (45.1% in the combined placebo group compared to 53.6% in the combined lixisenatide-treated groups), mainly related to an imbalance in the gastrointestinal events. The most commonly reported TEAE was nausea (4.1% in the combined placebo group, 24.2% in the lixisenatide 2-step titration arm, and 20.2% in the lixisenatide 1-step titration arm), coherent with the known safety profile of GLP-1 receptor agonists.

Six (6) cases of symptomatic hypoglycemia (per protocol definition) were observed during the study (2 [1.6%] in the combined placebo group, 3 [2.5%] in the lixisenatide 2-step titration arm, and 1 [0.8%] in the lixisenatide 1-step titration arm). None were severe per protocol definition.

Eleven (4.6%) patients in the combined lixisenatide-treated group reported injection site reaction; none of them led to treatment discontinuation. Two patients (0.8%) treated with lixisenatide had allergic reactions confirmed by the allergic reaction assessment committee. Neither reaction was serious and both events were considered to be related to the investigational product.

No cases of pancreatitis were reported during the study.

Concerning laboratory parameters, there were no relevant changes in any of the laboratory tests. No case of elevated lipase or amylase (≥3 x ULN) was observed in any of the treatment groups.

There were no relevant changes in systolic and diastolic blood pressure, heart rate, or ECG parameters.

Anti-lixisenatide antibody data

At Baseline, a few patients were already reported as antibody-positive, with concentrations below the lower limit of quantification (LLOQ) in all cases. This percentage increased with time, and was 55% to 60% after 12 weeks of lixisenatide-treatment. No significant differences in adverse events were observed between the antibody-positive and antibody-negative patient population.

The antibody concentration was below the quantification limit (LLOQ) in majority of the antibody-positive patients at baseline (out of 11 patients, 9 patients had concentrations of <LLOQ, 1 patient had >LLOQ, and 1 patient had no antibody concentration reported at baseline), and also (with 3 exceptions) at Week 2. At Week 4, in about two-thirds of the antibody-positive patients, the antibody concentration could be determined (geometric mean: 32.942 nmol/L and 20.679 nmol/L in the 2-step and 1-step titration arms, respectively). At Week 12, this concentration decreased to a geometric mean below 15 nmol/L in both lixisenatide-treated arms.

Pharmacokinetic results:

In patients who were anti-lixisenatide antibody-negative, and who were treated with 20 µg lixisenatide per day, the median post-injection concentration of lixisenatide was approximately 60 pg/mL (59.70, 56.35, and 55.25 pg/mL at Weeks 2, 4, and 12), respectively; the median pre-injection concentration was less than the lower limit of quantification (LLOQ) for all 3 visits. In antibody-positive patients these values remarkably increased with the duration of treatment to 71.45, 125.0, and 451.0 pg/mL at Weeks 2, 4, and 12, respectively (post-injection), and to 190.5 pg/mL at Week 12 already pre-injection. The biologically active concentration (predose) was above LLOQ (40 pg/mL) in 34 of 81 patients being reported as antibody-positive at the end of study (Week 12), with a geometric mean of 122 pg/mL; the other samples were below 40 pg/mL.

Conclusions: [redacted]

Date of report: 04-Aug-2011