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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): Lixisenatide (AVE0010)	Study Identifiers: NCT00976937, EudraCT 2008-007-334-22 Study code: EFC10780

Title of the study: A randomized, double-blind, double-dummy, 2-arm parallel-group, multicenter 24-week study comparing the efficacy and safety of AVE0010 to sitagliptin as add-on to metformin in obese type 2 diabetic patients younger than 50 and not adequately controlled with metformin (EFC10780)

Study center(s): Multicenter (92 centers in 13 countries)

Study period:

Date first patient enrolled: 31/Aug/2009

Date last patient completed: 19/Mar/2011

Phase of development: Phase 3

Objectives:

Primary: To assess the efficacy of AVE0010 (hereinafter referred to by the international nonproprietary name, lixisenatide) on a composite endpoint of glycemic control (glycosylated hemoglobin [HbA_{1c}]) and body weight, in comparison to sitagliptin as an add-on treatment to metformin, over a period of 24 weeks in obese type 2 diabetic patients younger than 50.

Secondary:
To assess the effects of lixisenatide on:
- Absolute changes in HbA_{1c} values and body weight,
- Fasting plasma glucose (FPG)
- Plasma glucose, insulin, C-peptide, glucagon, and proinsulin during a 2-hour standardized meal test,
- Insulin resistance assessed by homeostatic model assessment of insulin resistance (HOMA-IR)
- Beta cell function assessed by homeostatic model assessment of β-cell function (HOMA-β);

To assess lixisenatide safety and tolerability;
To assess anti-lixisenatide antibody development.

Methodology: This was a randomized, double-blind, double-dummy, 2-arm, balanced, parallel-group, active comparator-controlled multicenter 24-week study, with a 2-step dose increase regimen for lixisenatide or volume-matched placebo (10 µg injection once daily [QD] for 1 week, then 15 µg QD for 1 week, followed by the maintenance dose of 20 µg QD). Sitagliptin (and matching placebo) was provided as a 100 mg tablet for QD oral administration. Patients received either lixisenatide and sitagliptin-matched placebo or sitagliptin and lixisenatide-matched placebo. The study was double-blind with regard to treatment group. However, for lixisenatide or volume-matched placebo the injected volume differed according to the dose being received (dose increase or maintenance period) and therefore was not blinded.

Number of patients:

Planned: 300

Randomized: 319

Treated: 319

Evaluated:

Efficacy: 319

Safety: 319

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; obese (body mass index [BMI] ≥30 kg/m^2); aged from 18 years to less than 50 years; and HbA_{1c} ≥7.0% and ≤10% at screening.

Study treatments

Investigational medicinal product(s): lixisenatide; sitagliptin-matched placebo

Formulation: 10 µg, 15 µg, and 20 µg; 100 mg

Route of administration: subcutaneous injection; oral

Reference therapy: sitagliptin; lixsenatide-matched placebo

Formulation: 100 mg; 10 µg, 15 µg, and 20 µg

Route(s) of administration: oral; subcutaneous injection

Duration of treatment: 24 weeks

Duration of observation: Maximum duration of 27 weeks ±10 days (3-week screening + 24-week double-blind, double-dummy, active-controlled treatment + 3-days follow-up)

Criteria for evaluation:

Efficacy: Efficacy was assessed using the following criteria: the percentage of patients with HbA_{1c} <7.0% and a weight loss of at least 5% of baseline body weight at Week 24 (primary efficacy variable); the absolute change in HbA_{1c} and body weight from baseline to Week 24; the percentage of patients with HbA_{1c} values ≤6.5% at Week 24, the percentage of patients with HbA_{1c} values <7.0% at Week 24, the percentage of patient with ≥5% weight loss (kg) from baseline to Week 24; the changes in FPG, insulin resistance (assessed by HOMA-IR), and β-cell function (assessed by HOMA-β) from baseline to Week 24; the change in 2-hour postprandial plasma glucose (PPG) after a standardized meal from baseline to Week 24; the change in glucose excursion after a standardized meal from baseline to Week 24; the change from baseline to Week 24 in insulin, C-peptide, glucagon, proinsulin, and proinsulin-to-insulin ratio under fasting and under 2-hour postprandial conditions after a standardized meal; 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-emergence 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 24. The samples were taken in the morning, before the injection of the investigational product. In vitro active concentration of lixisenatide was also determined 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") and received at least 1 dose of double-blind investigational product.

The primary efficacy endpoint (the percentage of patients with HbA_{1c} <7% and weight loss of at least 5% of baseline body weight at Week 24) was analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%] and screening BMI [<35, ≥35 kg/m^2]). The p-value based on the CMH test is provided. The point of estimate of the treatment difference (lixisenatide compared with sitagliptin) in proportion as well as the associated 95% confidence interval (CI) is provided based on the weighted average of treatment differences from each strata using CMH weights.

As supportive analysis, the odds ratio of lixisenatide to sitagliptin was assessed using a logistic regression (asymptomatic). The model included treatment groups, randomization strata of screening HbA_{1c} (<8.0%, ≥8.0%), and randomization strata of screening BMI (<35 kg/m^2, ≥35 kg/m^2) as fixed effects, and baseline HbA_{1c} and baseline body weight values as covariates. The adjusted odds ratio and the associated 95% CI are provided.

No multiplicity adjustment was made on the secondary efficacy endpoints. Data for all continuous secondary efficacy endpoints (eg, the absolute change in HbA_{1c} from baseline to Week 24) were analyzed using an analysis of covariance model with treatment (lixisenatide or sitagliptin), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%], screening BMI [<35 kg/m^2, ≥35 kg/m^2]), and country as fixed effects, with the corresponding baseline value as a covariate. The adjusted treatment mean estimates with standard errors, the adjusted estimate of treatment mean difference (between lixisenatide and sitagliptin) with standard errors, and associated 95% CIs are provided. Data for the categorical secondary efficacy endpoints (eg, the percentage of patients with HbA_{1c} <7.0% or with HbA_{1c} ≤6.5% at Week 24) were evaluated by descriptive statistics.

In addition, the point estimates of the treatment differences (lixisenatide versus sitagliptin) in proportions as well as the associated 95% CIs are provided based on the weighted average of treatment differences from each stratum using CMH weights for the categorical secondary efficacy endpoints.

Safety: The safety population was the total treated population, defined as all patients randomized (via the central randomization system, according to the protocol) 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, and the biologically active concentration of lixisenatide were listed and summarized using descriptive statistics. These data will be reported in an amended version of this report.

Summary:

Efficacy results: The percentage of patients who met the criteria for the primary efficacy endpoint (the percentage of patients with HbA_{1c} <7.0% and a weight loss of at least 5% of baseline body weight at Week 24) was higher in the lixisenatide treatment group (19 patients [12.0%]) compared with the sitagliptin treatment group (12 patients [7.5%]). However, based on the prespecified primary analysis, no statistically significant difference was seen between the 2 treatment groups: the weighted average of difference in response rate versus sitagliptin was 4.6% (95% CI: -1.84%, 11.00%; p = 0.1696).

No significant difference was seen between the 2 treatment groups in the least squares (LS) mean HbA_{1c} changes from baseline to Week 24 (-0.66% and -0.72% in the lixisenatide and sitagliptin treatment groups, respectively); the LS mean difference versus sitagliptin was 0.06% (95% CI: -0.179, 0.308).

At Week 24, a similar percentage of patients in both treatment groups had achieved HbA_{1c} values ≤6.5% (24.0% of patients in the lixisenatide treatment group and 26.3% of patients in the sitagliptin treatment group) or <7.0% (40.7% of patients in the lixisenatide group and 40.0% of patients in the sitagliptin group).

Patients treated with lixisenatide had significantly greater body weight loss than patients treated with sitagliptin (LS mean body weight loss from baseline to Week 24 was -2.51 kg compared with -1.17 kg, respectively); LS mean treatment difference versus sitagliptin: -1.34; 95% CI: -2.101, -0.575. More lixisenatide-treated patients (28 patients [18.4%]) compared with sitagliptin-treated patients (19 patients [11.9%]) had ≥5% body weight loss from baseline to Week 24.

No significant difference was observed between the lixisenatide and sitagliptin treatment groups in FPG levels.

Treatment with lixisenatide significantly improved postprandial glycemic control after a standardized meal in comparison with sitagliptin (in terms of PPG and glucose excursion). The LS mean change from baseline to Week 24 in 2-hour PPG was -3.35 mmol/L in the lixisenatide treatment group compared with -1.44 mmol/L in the sitagliptin treatment group (LS mean difference versus sitagliptin: -1.91 mmol/L; 95% CI: -2.876, -0.941). The LS mean change from baseline to Week 24 in glucose excursion was -2.55 mmol/L and -0.42 mmol/L in the lixisenatide and sitagliptin treatment groups, respectively. The LS mean difference for lixisenatide versus sitagliptin was -2.13 mmol/L (95% CI: -2.819, -1.434).

No significant difference was observed between the lixisenatide and sitagliptin treatment groups in insulin resistance assessed by HOMA-IR or β-cell function assessed by HOMA-β. No relevant differences were observed between the lixisenatide and sitagliptin treatment groups in the secondary parameters of plasma insulin levels, proinsulin levels, C-peptide levels, and glucagon levels. A significant treatment difference was observed for the fasting proinsulin-to-insulin ratio. The LS mean difference for lixisenatide versus sitagliptin was 0.08 (95% CI: 0.001, 0.167).

The percentages of patients requiring rescue therapy were low and not significantly different between the 2 treatment groups (9.5% in the lixisenatide group and 6.8% in the sitagliptin group).

Safety results: An overview of the safety results observed during the study is provided in the following table. The proportion of patients who experienced TEAEs during the study was similar in the 2 treatment groups. No patient died during the study. Six patients had serious TEAEs during the on-treatment period, 3 patients (1.9%) in each treatment group. The percentage of patients with TEAEs leading to treatment discontinuation was low and similar between the lixisenatide-treated and sitagliptin-treated patients (2.5% and 3.1%, respectively).

	Lixisenatide (N=158)	Sitagliptin (N=161)
Patients with any TEAE	101 (63.9%)	98 (60.9%)
Patients with any serious TEAE	3 (1.9%)	3 (1.9%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	4 (2.5%)	5 (3.1%)

TEAE: Treatment Emergent Adverse Event

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

Nausea was the most frequently reported TEAE in the lixisenatide treatment group, which is consistent with the known safety profile of glucagon-like peptide-1 receptor agonists; this study TEAE was reported more frequently in the lixisenatide treatment group (28 patients [17.7%]) compared with the sitagliptin treatment group (11 patients [6.8%]). The most commonly reported TEAE in the sitagliptin treatment group was headache (15 patients [9.3%]) compared with the lixisenatide treatment group (20 patients [12.7%]).

A similar percentage of patients had symptomatic hypoglycemia, per protocol definition, in the lixisenatide treatment group (1 patient [0.6%]) compared with the sitagliptin treatment group (3 patients [1.9%]). No events of severe symptomatic hypoglycemia were reported during the study.

Injection site reactions were reported in 9 patients (5.7%) in the lixisenatide treatment group and in 2 patients (1.2%) in the sitagliptin treatment group. None of these events were serious or resulted study treatment discontinuation.

Three patients (2 patients [1.3%] and 1 patient [0.6%] in the lixisenatide and sitagliptin treatment groups, respectively) had a TEAE adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee. Only 1 of these events was adjudicated as possibly related to study treatment (anaphylactic reaction Grade 3 in the lixisenatide group). The patient recovered 2 hours after AE onset with corrective treatment and was discontinued from study treatment.

Six patients (3.8%) in the lixisenatide treatment group and 2 patients (1.2%) in the sitagliptin treatment group had events of changes in pancreatic enzymes, lipase, or amylase reported on the electronic case report form (eCRF) AE form specific for “suspected pancreatitis”. No confirmed diagnoses of pancreatitis were reported during the study. None of the events were serious, severe in intensity, or led to permanent discontinuation of treatment.

One patient (0.6%), in the sitagliptin treatment group, had a TEAE of blood calcitonin increased (calcitonin levels ≥20 ng/L but <50 ng/L), and the event was not serious.

There were no relevant changes in any of the laboratory tests. There were minimal changes in heart rate and systolic and diastolic blood pressure in both treatment groups during the study. The assessment of ECG readings did not reveal any clinically meaningful abnormalities.

Issue date: 29-Jan-2014