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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: NCT01169779, U1111-1116-8938 Study code: EFC11321
Title of the study: Efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus insufficiently controlled by metformin (with or without sulfonylurea): a multicenter, randomized, double-blind, parallel-group, placebo-controlled study with 24-week treatment period (EFC11321).	
Study center(s): Multicenter (37 centers in 4 countries or areas).	
Study period: Date first patient enrolled: 21/Jul/2010 Date last patient completed: 22/Dec/2011	
Phase of development: Phase 3	

Objectives:

Primary: To assess the effects on glycemic control of AVE0010 (hereinafter referred to by the international nonproprietary name, lixisenatide) in comparison to placebo as an add-on treatment to metformin with or without sulfonylurea in terms of glycosylated hemoglobin (HbA_{1c}) reduction over a period of 24 weeks in patients with type 2 diabetes.

Secondary:

- To assess the effects of lixisenatide over 24 weeks on:
  - Percentage of patients reaching HbA_{1c} <7% or HbA_{1c} ≤6.5%.
  - Fasting plasma glucose (FPG).
  - Two-hour postprandial plasma glucose (PPG) and glucose excursion during standardized meal test (approximately 50% of all randomized patients).
  - Body weight.
- To assess lixisenatide safety and tolerability.
- To assess lixisenatide pharmacokinetic and antilixisenatide antibody development.

Methodology: Randomized, double-blind, placebo-controlled, 2-arm parallel-group study with a 1-week single-blind placebo run-in and a double-blind treatment period with a 1-step titration regimen (10 µg once daily for 2 weeks followed by the maintenance dose of 20 µg). Randomization was stratified by HbA_{1c} (<8%, ≥8%) and sulfonylurea use (Yes, No) at screening.

Number of patients:	
Planned:	380 (190 per treatment arm)
	Randomized: 391
	Treated: 390
Evaluated:	
	Efficacy: 388
	Safety: 390

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 alone at a stable dose of at least 1.0 g/day and not more than 1.5 g/day, or in combination with sulfonylurea at a stable dose of at least the maximal effective dose (ie, half of the maximum recommended dose according to local labeling) for at least 3 months prior to screening; and HbA_{1c} ≥7% and ≤10% at screening.

Study treatments

Investigational medicinal product(s): Lixisenatide

Formulation: 3-mL aqueous injection (cartridge) containing the active ingredient 300 µg (ie, 100 µg/mL), sodium acetate trihydrate, meta-cresol, glycerol, L-methionine, hydrochloric acid/sodium hydroxide, water for injection.

Route(s) of administration: subcutaneous injection using a pen-type injector (OptiClik®)

Dose regimen: 10 µg titration dose for 2 weeks followed by 20 µg maintenance dose up to the end of the double-blind treatment period

Reference therapy: Placebo

Formulation: 3-mL aqueous injection (cartridge)

Route of administration: Subcutaneous injection using a pen-type injector (OptiClik®)

Dose regimen: 10 µg titration dose for 2 weeks followed by 20 µg maintenance dose up to the end of the double-blind treatment period.

Noninvestigational medicinal product(s): Metformin or metformin plus sulfonylurea

Formulation: Tablet

Route(s) of administration: Oral

Dose regimen: As prescribed (at least 1.0 g/day and not more than 1.5 g/day for metformin; at least the maximal effective dose [ie, half of the maximum recommended dose according to local labeling] for sulfonylurea)

Duration of treatment: 24 weeks

Duration of observation: 27 weeks ±10 days (up to 2 weeks screening + 1 week run-in + 24 weeks double-blind treatment + 3 days follow-up)

Criteria for evaluation:

Efficacy: Efficacy was assessed using the following criteria: the absolute change of HbA_{1c} from baseline to Week 24; the percentage of patients with HbA_{1c} <7% and ≤6.5% at Week 24; the change in 2-hour PPG and glucose excursion after a standardized meal test from baseline to Week 24; the changes in FPG and body weight from baseline to Week 24; the percentage of patients requiring rescue therapy during the 24-week treatment period; and the percentage of patients with ≥5% weight loss from baseline to Week 24.

Safety: Occurrence of adverse events (AEs), particularly treatment-emergent adverse events (TEAEs) and serious adverse events, symptomatic hypoglycemia, signs of local intolerability, allergic or allergic-like reactions, suspected pancreatitis, and major cardiovascular events; clinical laboratory (including, in particular, amylase, lipase, and calcitonin); vital signs (blood pressure and heart rate); 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.

Pharmacokinetics: Samples for assessment of plasma concentrations of total lixisenatide were taken at Weeks 2, 24, before the start of rescue therapy, and at the end of treatment. Samples were taken to determine the active concentration (predose) at Weeks 2, 4, and 24, and in addition, both prior to rescue therapy and at the end of treatment, if this was before 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 of screening HbA_{1c} (<8.0%, ≥8.0%) and sulfonylurea 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 to be performed to test the secondary efficacy variables (change in 2 hour PPG after a standardized meal from baseline to Week 24; FPG and body weight from baseline to Week 24; and the percentage of patients requiring rescue therapy during the double-blind on-treatment period). The test was to be 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, on-treatment period) were analyzed using a Cochran-Mantel-Haenszel method.

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, according to the treatment actually received. 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 concerning cross-reactivity of the antibodies with endogenous glucagon-like peptide 1 (GLP-1) and glucagon 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 -0.83% and -0.47% in the lixisenatide and placebo treatment groups, respectively). The LS mean difference for lixisenatide versus placebo was -0.36% (p = 0.0004). The superiority of lixisenatide was consistently observed within the subgroup analyses for change in mean HbA_{1c} by baseline factors. At Week 24, the percentage of patients reaching the HbA_{1c} target of ≤6.5% or <7%, was also significantly higher in the lixisenatide treatment group (32.4% for HbA_{1c} ≤6.5% and 53.0% for HbA_{1c} <7%) versus the placebo treatment group HbA_{1c} ≤6.5% and 38.8% for HbA_{1c} <7%) (p = 0.0010 for HbA1c ≤6.5% and p = 0.0030 for HbA_{1c} <7%). There were no substantial differences in mean HbA_{1c} change from baseline between the antibody-positive and antibody-negative patients.

The LS mean change in 2-hour PPG after a standardized meal from baseline to Week 24 was -5.61 mmol/L in the lixisenatide treatment group compared with -1.33 mmol/L in the placebo treatment group; the LS mean difference between the 2 treatment groups (-4.28 mmol/L) was statistically significant (95% confidence interval [CI]: -5.359, -3.201; p <0.0001). Furthermore, the LS mean change from baseline to Week 24 in glucose excursion was -4.78 mmol/L in the lixisenatide treatment group compared with -0.79 mmol/L in the placebo treatment group, and the LS mean difference between the 2 treatment groups was 3.99 mmol/L (95% CI: -4.969, -3.010).

The LS mean change in FPG from baseline to Week 24 was -0.69 mmol/L in the lixisenatide treatment group compared with 0.21 mmol/L in the placebo treatment group; the LS mean difference between the 2 treatment groups was statistically significant (-0.48 mmol/L; 95% CI: -0.845, -0.111; p = 0.0109).

The LS mean body weight loss from baseline to Week 24 was 1.50 kg in the lixisenatide treatment group and 1.24 kg in the placebo treatment group; the LS mean difference between the 2 treatment groups was not statistically significant: -0.27 kg (95% CI: -0.776, 0.237; p = 0.2960).

The percentage of patients requiring rescue therapy during the on-treatment period was small in the 2 treatment groups (3.6% and 6.7% in the lixisenatide and placebo treatment groups, respectively).

Safety results:

An overview of the safety results observed during the whole study is provided in the following table. Seven patients had serious TEAEs during the on-treatment period (3 patients [1.5%] and 4 patients [2.1%] in the lixisenatide and placebo treatment groups, respectively). No patients died during the study. A total of 14 patients (11 patients [5.6%] in the lixisenatide treatment group and 3 patients [1.5%] in the placebo treatment group) permanently discontinued study treatment due to TEAEs; this difference was mainly due to the higher frequency of gastrointestinal TEAEs in the lixisenatide treatment group. Nausea and vomiting were the most common TEAEs leading to treatment discontinuation in the lixisenatide treatment group (3 patients [1.5%] and 2 patients [1.0%], respectively), while no patient discontinued treatment due to either nausea or vomiting in the placebo treatment group. No individual TEAE (by preferred term [PT]) led to more than 1 patient permanently discontinuing treatment in the placebo treatment group.

	Placebo (N=194)	Lixisenatide (N=196)
Patients with any TEAE	92 (47.4%)	126 (64.3%)
Patients with any serious TEAE	4 (2.1%)	3 (1.5%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	3 (1.5%)	11 (5.6%)

TEAE: Treatment Emergent Adverse Event

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

Note: On-treatment period = the time from the first dose of double-blind investigational product up to 3 days after the last dose administration.

The incidence of TEAEs was higher in the lixisenatide-treated group compared with the placebo-treated group (64.3% and 47.4%, respectively). The most commonly reported TEAE in the lixisenatide treatment group was nausea (16.3% and 2.6% in the lixisenatide and placebo treatment groups, respectively), which is consistent with the known safety profile of GLP-1 receptor agonists; most of the events were mild to moderate in intensity and most patients recovered without the need to administer corrective treatment. This was followed by hypoglycemia (9.2% and 4.6% in the lixisenatide and placebo treatment groups, respectively), dizziness (8.7% and 4.1% in the lixisenatide and placebo treatment groups, respectively), and vomiting (7.7% and 1.0% in the lixisenatide and placebo treatment groups, respectively). Diabetic nephropathy was the most common TEAE in the placebo treatment group (6.6% and 6.7% in the lixisenatide and placebo treatment groups, respectively).

The number (percentage) of patients who had symptomatic hypoglycemia fulfilling the protocol definition during the study was 11 patients (5.6%) in the lixisenatide treatment group and 5 patients (2.6%) in the placebo treatment group. The incidence rates of symptomatic hypoglycemia with blood glucose <60 mg/dL were exactly the same in the 2 treatment groups (3 patients [1.5%] in each group). In addition, the number of hypoglycemic events, with blood glucose <60 mg/dL, per 100 patient years was 8.0 events in the lixisenatide treatment group and 7.8 events 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 5 patients (2.6%) in the lixisenatide treatment group and 2 patients (1.0%) 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. Of the 5 patients in the lixisenatide treatment group, the injection site reaction for 4 patients (2.0%) was assessed by the Allergic Reaction Assessment Committee (ARAC). One of these 4 patients had an injection site reaction that was also confirmed as an allergic reaction by the ARAC.

Three patients (2 patients [1.0%] and 1 patient [0.5%] in the lixisenatide and placebo treatment groups, respectively) had a TEAE adjudicated as an allergic reaction by the ARAC. Two events from 2 patients (anaphylactic shock and injection site reaction) in the lixisenatide treatment group were adjudicated as possibly related to investigational product. The event of anaphylactic shock led to permanent discontinuation of study treatment; this event occurred after the first injection of lixisenatide and was considered to be an anaphylactoid reaction by the ARAC chairman.

No patient in either treatment group had any events of increases in pancreatic enzymes, lipase, or amylase reported in the electronic case report form (eCRF) AE form specific for “suspected pancreatitis” during the on-treatment period; there was also no confirmed diagnosis of pancreatitis. In addition, no TEAEs of blood calcitonin increased and no thyroid-related events were reported for any patient during the on-treatment period.

A similar percentage of patients in each treatment group had a cardiac disorder TEAE (3 patients [1.5%] in the lixisenatide treatment group and 4 patients [2.1%] in the placebo treatment group); 3 of these patients (1 patient [0.5%] in the lixisenatide treatment group and 2 patients [1.0%] in the placebo treatment group) had a coronary artery disorders TEAE. For 1 patient in the lixisenatide treatment group, the coronary artery disorders TEAE (acute myocardial infarction) was serious and 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, 13 patients (6.8%) treated with lixisenatide and 7 patients (3.7%) treated with placebo were already antibody-positive. The percentage of patients who were antibody-positive in the lixisenatide treatment group increased with time, and was 67.2% at Week 24.

The antibody concentration was below the lower limit of quantification (LLOQ; 3.21 nmol/L) in more than half of the antibody-positive patients in the lixisenatide treatment group, at all timepoints.

Cross-reactivity of the antibodies with endogenous GLP-1, as well as glucagon, was not seen in any of the patients.

Overall, there was no substantial difference in the TEAE profile between the antibody-positive and 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 1 to 2 hour and 4 to 6 hour postinjection concentrations of lixisenatide were 95.80 pg/mL and 64.20 pg/mL, respectively, at Week 2, and 104.00 pg/mL and 75.00 pg/mL, respectively, at Week 24. The respective medians at predose were below the LLOQ at both visits.

In patients who were anti-lixisenatide antibody-positive, and who were treated with 20 µg lixisenatide per day, the median 1 to 2 hour and 4 to 6 hour postinjection concentrations of lixisenatide increased with time and were 133.00 pg/mL and 136.00 pg/Ml, respectively, at Week 2, and 332.50 pg/mL and 274.00 pg/mL, respectively, at Week 24. The median at predose was below the LLOQ at Week 2, and was 91.55 pg/mL at Week 24.

The biologically active concentration (predose) was below 40 pg/mL (LLOQ) in more than half of the samples with a known antibody-positive status, at all timepoints. At Week 24, 40/117 (34%) of the anti-lixisenatide positive samples were above the LLOQ, with a median active concentration of 114.75 pg/mL. The median of the active fraction (ratio: active lixisenatide concentration/total lixisenatide concentration) for these patients was 0.254 (Week 24).

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