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Sponsor / Company: Sanofi Drug substance(s): Lixisenatide (AVE0010)	Study Identifiers: NCT00905255 Study code: LTS10888
Title of the study: A randomized, open label, parallel-group (one-step titration and two-step titration), multicenter 52-week study followed by a 24-week extension assessing the safety and tolerability of AVE0010 monotherapy in patients with type 2 diabetes	
Study center(s): Multicenter (9 centers in Japan)	
Study period: Date first patient enrolled: 09/May/2009 Date last patient completed: 22/Jan/2011	
Phase of development: Phase 3	

Objectives:

Primary:

- To assess the safety of AVE0010 (hereinafter referred to by the International Nonproprietary Name, lixisenatide) once daily (QD) treatment in monotherapy at Week 24 by a descriptive comparison of a 1-step titration and a 2-step titration regimen in patients with type 2 diabetes in Japan.

Secondary:

- To assess the overall safety of lixisenatide QD treatment in monotherapy at Week 52 and Week 76 in patients with type 2 diabetes in Japan
- To assess the effects of lixisenatide on:
  - Glycosylated hemoglobin (HbA_{1c}) reduction over a period of 52 weeks and 76 weeks
  - Body weight
  - Fasting plasma glucose (FPG).
- To assess lixisenatide pharmacokinetics (PK) (Weeks 2, 24, 52, and 76) and anti-lixisenatide antibody (baseline, Weeks 2, 4, 24, 52, and 76).

Note: Analysis for the 76-week treatment period was added in the efficacy and safety analyses before database lock per the amended statistical analysis plan, since the study period was extended from 52 weeks to 76 weeks as part of a protocol amendment.

Methodology: This was a randomized, open-label, 2-arm, parallel-group, multicenter study, comparing a 2-step titration regimen (10 µg injection QD for 1 week, then 15 µg QD for 1 week, followed by the maintenance dose of 20 µg QD) and a 1-step titration regimen (10 µg injection QD for 2 weeks, followed by the maintenance dose of 20 µg QD) for lixisenatide.

Number of patients:	Planned: 66
	Randomized: 69
	Treated: 69
Evaluated:	
	Efficacy: 69
	Safety: 69
	Pharmacokinetics: 69

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus (T2DM) diagnosed at least 2 months before the screening visit; not treated by an antidiabetic agent in the 3 months before screening (except treatment with sulfonylureas or α-glucosidase inhibitors at a stable dose. In this case, the oral antidiabetic agent must have been discontinued before starting the single-blind run-in phase); and HbA_{1c} ≥7.0% and ≤10.0% at screening.

Study treatments

Investigational medicinal product(s): placebo (at run-in only); lixisenatide

Dose: 0 µg (at run-in only); 10 µg, 15 µg, and 20 µg

Route(s) of administration: Subcutaneous injection

Duration of treatment: 76 weeks (52-week open-label treatment; 24-week open-label extension period)

Duration of observation: 79 weeks±12 days (up to 2 weeks screening + 1 week run-in + 52-week open-label treatment + 24-week open-label extension period + 3 days follow-up)

Criteria for evaluation: This study was a safety study. Efficacy was only evaluated as a secondary objective.

Efficacy: Efficacy was assessed using the following criteria: the change in HbA_{1c}, body weight, and FPG from baseline to Week 24, Week 52, and Week 76; the percentage of patients with HbA_{1c} values <7.0% or HbA_{1c} values ≤6.5% at Week 24, Week 52, and Week 76; and the percentage of patients requiring rescue therapy during the treatment period.

Safety:

Primary endpoint(s): Overall safety (adverse events [AEs], serious AEs, symptomatic hypoglycemia, local tolerability at injection site, allergic reactions, suspected pancreatitis, major cardiovascular events, vital signs [blood pressure and heart rate], electrocardiograms [ECGs], hematology, serum chemistry, amylase, lipase, lipid parameters, calcitonin, and microalbuminuria) for each 1-step and 2-step titration group at Week 24.

Secondary endpoints: Overall safety at Week 52 and Week 76.

Anti-lixisenatide antibody assessments: The status and concentration of anti-lixisenatide antibodies were determined at baseline, at Weeks 2, 4, 24, 52, 76, and (if applicable) at the visit before rescue therapy. 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 0.5 to 2 hours predose and 2.5 to 4 hours postdose at Week 2, Week 24, Week 52 , Week 76, and (if applicable) at the visit before rescue therapy. In vitro active concentration of lixisenatide was also determined.

Statistical methods:

Efficacy: As this was a safety study, the efficacy of lixisenatide was assessed only descriptively using the modified intent-to-treat population, 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 efficacy variable, irrespective of compliance with the study protocol and procedures.

No formal statistical testing was performed for any of the efficacy endpoints. All efficacy analyses were presented for the overall group (pooled titration group). The summaries of efficacy data were also provided for the 2-step titration group and 1-step titration group, and the overall group, as applicable. Descriptive statistics were provided for all continuous variables at the scheduled visits and change from baseline at each visit point (last observation carried forward at Week 52 and Week 76). The 95% confidence intervals with descriptive statistics were provided for the changes at each visit within the group. Categorical analyses were performed on HbA_{1c} levels (ie, the percentage of patients with HbA_{1c} values <7.0% and ≤6.5% at Week 24, Week 52, or Week 76, respectively). The percentage of patients requiring rescue therapy during the treatment period was also provided.

Safety: Assessment of safety was the primary objective of this study. The safety population was the total treated population, defined as all patients who were randomized (via the central randomization system, according to the protocol) and took at least 1 dose of open-label investigational product, regardless of the amount of treatment administered. The evaluation of AEs, clinical laboratory data, vital signs, and ECG data was descriptive.

The primary analyses and assessment of the safety variables with 24-week data were performed for the 1-step and 2-step titration groups. The secondary analyses and assessment were performed on the pooled data of the 1-step and the 2-step titration groups overall based on the 52-week safety data or the 76-week safety data.

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: At Week 24, the mean (standard deviation [SD]) change from baseline in HbA_{1c} (%) using the observed cases was -0.99 (1.07) and -0.74 (0.79) for the 2-step and 1-step titration groups, respectively. This effect was maintained up to Week 76 (pooled titration group: -0.83 [0.96] at Week 52 and -0.72 [1.20] at Week 76). Corresponding with this, in the 2-step titration group, 4 patients (17.4%) achieved HbA_{1c} ≤6.5%, and 8 patients (34.8%) had HbA_{1c} <7.0% at Week 24. In the 1-step titration group, 5 patients (15.2%) achieved HbA_{1c} ≤6.5%, and 11 patients (33.3%) had HbA_{1c} <7.0% at Week 24. This effect was maintained in the pooled titration group throughout the whole 76-week study period.

At Week 24, the mean (SD) change from baseline in body weight (kg) using the observed cases was -0.43 (2.08) and -1.08 (1.66) for the 2-step and 1-step titration groups, respectively. This increased further to -1.67 (2.10) at Week 52 and -1.58 (2.15) at Week 76 (pooled titration group).

At Week 24, the mean (SD) change from baseline in FPG (mmol/L) using the observed cases was -1.16 (1.20) and -0.56 (1.54) for the 2-step and 1-step titration groups, respectively. The mean (SD) change from baseline in FPG for the pooled titration group was -0.96 (1.54) at Week 52 and -0.46 (2.08) at Week 76.

Five patients (15.2%) in the 2-step titration group required rescue therapy at Week 24, compared to 2 patients (5.6%) in the 1-step titration group. The number of patients in the pooled titration group requiring rescue therapy increased to 12 (17.4%) at Week 52 and to 16 (23.2%) at Week 76. As approximately 50% of patients were being treated with an oral antidiabetic agent that was stopped before run-in, and as the median duration of diabetes at screening (7.26 years) was relatively long for patients treated with either diet and exercise or diet and exercise in combination with a single oral antidiabetic agent, this finding was in line with the patient population.

Safety results: Median exposure was similar for the 2 titration groups (531.0 days and 533.0 days in the 2-step and 1-step titration groups, respectively). All but 1 of the 69 patients (2-step titration group) was at the target total daily dose of 20 µg at the end of the titration period. Most patients (53 patients [76.8%]) were at the target total daily dose of 20 µg at the end of the treatment period.

The proportion of patients with treatment-emergent adverse events (TEAEs) during the 24-week treatment period was generally comparable in both titration groups (27 patients [81.8%] for the 2-step titration group and 32 patients [88.9%] for the 1-step titration group). The number of patients with TEAEs in the pooled titration group was 61 patients (88.4%) during the 52-week treatment period and 63 patients (91.3%) during the whole 76-week treatment period.

No deaths were reported during the study. During the 24-week treatment period, 2 patients (6.1%) in the 2-step titration group had a serious TEAE; no serious TEAEs were reported in the 1-step titration group. The number of patients with serious TEAEs in the pooled titration group was 3 (4.3%) during both the 52-week and the 76-week treatment periods.

The number of patients with TEAEs leading to permanent treatment discontinuation during the 24-week treatment period was 3 (9.1%) in the 2-step titration group and 4 (11.1%) in the 1-step titration group. The number of patients with TEAEs leading to permanent treatment discontinuation during the whole 76-week treatment period in the pooled titration group was 10 (14.5%). An overview of the safety results observed during the whole study is provided in the following table.

	All (N=69)
Patients with any TEAE	63 (91.3%)
Patients with any serious TEAE	3 (4.3%)
Patients with any TEAE leading to death	0
Patients with any TEAE leading to permanent treatment discontinuation	10 (14.5%)

TEAE: Treatment Emergent Adverse Event.

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

The most frequently reported TEAE during the 24-week treatment period was nausea, which is consistent with the known safety profile of glucagon-like peptide 1 (GLP-1) receptor agonists. A lower percentage of patients in the 2-step titration group (12 patients [36.4%]) compared with 1-step titration group (18 patients [50.0%]) reported nausea. Similarly, nausea was the most frequently reported TEAE in the pooled titration group during the whole 76-week treatment period (30 patients [43.5%]); there was no increase in the number of patients with nausea between Week 24 and Week 76. Conversely, during the 24-week treatment period, the number of patients with vomiting was higher in the 2-step titration group (4 patients [12.1%]) compared with the 1-step titration group (1 patient [2.8%]); no additional patients had vomiting during the remainder of the 76-week treatment period. During the 24-week treatment period, diarrhea was reported for 1 patient (3.0%) and 3 patients (8.3%) in the 2-step and 1-step titration groups, respectively; and no additional patients had diarrhea during the remainder of the 76-week treatment period.

Two patients (6.1%) in the 2-step titration group and 1 patient (2.8%) in the 1-step titration group had symptomatic hypoglycemia per protocol definition during the 24-week treatment period. The number of patients with symptomatic hypoglycemia in the pooled titration group was 5 (7.2%) during the 52-week and 76-week treatment periods. None of the events of symptomatic hypoglycemia reported during the study were considered severe according to the protocol-defined criteria.

The number of patients with injection site reactions during the 24-week treatment period was 7 (10.1%); 3 patients (9.1 %) in the 2-step titration group and 4 patients (11.1 %) in the 1-step titration group. No additional patients had injection site reactions during the remainder of the 76-week treatment period. None of the events of injection site reaction reported during the study was considered severe in intensity or led to discontinuation of treatment.

The number of patients with a TEAE adjudicated as an allergic reaction considered possibly related to investigational product by the Allergic Reaction Assessment Committee (ARAC) during the 24-week, 52-week, and 76-week treatment periods was low, with 1 event of urticaria (2.6%) in the 1-step titration group. This TEAE of urticaria led to permanent discontinuation of study treatment.

There were no relevant changes in any of the laboratory tests. No patients had elevated lipase or amylase ≥3 x upper limit of normal (ULN). The overall incidence of calcitonin levels >ULN was low and similar for the 2 titration groups; none of the patients had a calcitonin level ≥20 ng/L. Slight decreases in systolic and diastolic blood pressure were observed (–1.1 mmHg and –0.3 mmHg from baseline to the last on-treatment value, respectively). There was minimal change in heart rate from baseline to the last on-treatment value (mean change: 1.3 beats/minute). No abnormal ECGs were considered to be clinically significant during the study.
Pharmacokinetic results: These data will be reported in an amended version of this clinical study report.
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