These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** AVE0010 (lixisentaide)	**Study Identifiers:** NCT01632163, UTN U1111-1124-1213 **Study code:** EFC12382
Title of the study: A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of lixisenatide in patients with type 2 diabetes insufficiently controlled with basal insulin with or without metformin	
Study center(s): 51 centers in total, China: 30; India: 10; Korea: 6; Russia: 5	
Study period: Date first patient enrolled: 30/Oct/2012 Date last patient completed: 16/May/2015	
Phase of development: Phase 3	

Objectives:

Primary

The primary objective of this study was to assess the effects on glycemic control of lixisenatide in comparison to placebo as an add-on treatment to basal insulin with or without metformin in terms of glycated hemoglobin A_{1c} (HbA_{1c}) reduction over a period of 24 weeks in insufficiently controlled type 2 diabetic patients.

Secondary

To assess the effects of lixisenatide over 24 weeks on:
Percentage of patients reaching HbA_{1c} <7% or ≤6.5%;
2-hour postprandial plasma glucose (PPG) and plasma glucose (PG) excursions during standardized meal challenge test;
Fasting plasma glucose (FPG);
Change in 7-point self-monitored plasma glucose (SMPG) profile;
Body weight;
Change in daily basal insulin doses;
Percentage of patients with HbA_{1c} <7% and no symptomatic hypoglycemia, percentage of patients with HbA_{1c} <7% and no body weight gain, and percentage of patients with HbA_{1c} <7% and no symptomatic hypoglycemia and no body weight gain.
To assess lixisenatide safety and tolerability.
To assess anti-lixisenatide antibody (anti-drug antibody, ADA) development.

Methodology: This was a double-blind, 1:1 randomized, placebo-controlled, 2-arm parallel group, multicenter, multinational study. The randomization was stratified by HbA_{1c} (<8%, ≥8%) at Visit 9 (Week -1) and metformin use (yes, no) at screening.

The study comprised 3 periods: A screening period up to 10 weeks, which included a screening Phase up to 2 weeks and a run-in Phase for forced titration of basal insulin of 8 weeks; a 24-week randomized double-blind treatment period; and a 3-day posttreatment safety follow-up period for all of the randomized patients after permanent study treatment discontinuation.

Number of patients**:**	Planned to screen: 750
	Screened: 789
	Randomized: 448
	Treated: 447
Evaluated:	
	Efficacy: 446
	Safety: 447

Diagnosis and criteria for inclusion:

Patients with type 2 diabetes mellitus (T2DM), diagnosed at least 1 year at the time of the screening visit, insufficiently controlled with basal insulin with or without metformin were enrolled. Patients with HbA_{1c} ≥7% and ≤10.5% at screening; Exclusion criteria: HbA_{1c} <7% or > 9.5% at Visit 9 (Week -1) or mean fasting SMPG calculated from the self-measurements for the week prior to randomization visit >140 mg/dL (7.8 mmol/L). Patients receiving basal insulin treatment not at a stable regimen for at least 3 months and/or not at a stable dose (±20%) of at least 15 U/day for at least 2 months prior to screening visit; metformin if given, not at a stable dose of at least 1.0 g/day for at least 3 months prior to screening visit were also excluded.

Study treatments

Investigational medicinal product(s): lixisenatide and placebo

Formulation:

Lixisenatide: sterile aqueous solution in a 3-mL glass cartridge containing 300 µg of the active ingredient (ie,100 µg/mL), glycerol, sodium acetate trihydrate, methionine, Meta-Cresol, HCl/NaOH, and water.

Placebo: a 3-mL glass cartridge containing aqueous solution.

Route(s) of administration: subcutaneous (SC) injection

Dose regimen: lixisenatide (or its placebo) was started at a dose of 10 µg once daily (QD) for 2 weeks, and then followed by a maintenance dose of 20 µg QD from Week 2 up to the end of the treatment period. If the target dose of 20 µg was not tolerated, lixisenatide or volume matched placebo could be down-titrated to 10 µg. Lixisenatide or matched placebo was administrated in the morning before breakfast.

Noninvestigational medicinal product(s):

Background therapies (basal insulin and metformin if applicable) were considered as noninvestigational medicinal products (NIMPs). During the 8-week run-in Phase, basal insulin was forced titrated individually once a week based on the results of the fasting SMPG levels, seeking a target between 80 mg/dL (4.4 mmol/L) and 100 mg/dL (5.6 mmol/L). If HbA_{1c} at Week -1 was ≥7% but ≤7.5%, the daily dose of basal insulin was to be reduced by 20% at randomization in order to avoid hypoglycemia when starting the combination therapy with lixisenatide. After randomization, the regimen of basal insulin (the timing and frequency of injection, type of basal insulin) was maintained stable during the treatment period. The adjustment of basal insulin dose was to be within ±20%.

If metformin was given, it was to be continued at a stable dose of at least 1.0 g/day throughout the study.

No rescue therapy was used in the study. If no reason could be found for insufficient glucose control, or if appropriate actions fail to decrease FPG/HbA_{1c} under the threshold values, patients were to be withdrawn from the study.

Duration of treatment: 24 weeks

Duration of observation: Up to 241 days (34 weeks + 3 days) (screening: up to 10 weeks, treatment: 24 weeks, follow-up: 3 days).

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint:

Absolute change of HbA_{1c} from baseline to Week 24.

Secondary efficacy endpoints:

Percentage of patients with HbA_{1c} <7 % at Week 24;
Percentage of patients with HbA_{1c} ≤6.5 % at Week 24;
Change in 2-hour PPG and PG excursions during standardized meal test from baseline to Week 24;
Plasma glucose excursion was defined as (2-hour PPG – PG 30 minutes prior to the meal test before IMP administration).
Change in FPG from baseline to Week 24;
Change in 7-point SMPG profile (ie, the average and each time point of the 7 points) from baseline to Week 24;
Change in body weight from baseline to Week 24;
Change in total daily basal insulin dose from baseline to Week 24.

Exploratory efficacy endpoints:

Percentage of patients with HbA_{1c} <7% and no experience of confirmed (PG <60 mg/dL [<3.33 mmol/L]) symptomatic hypoglycemia during the 24-week treatment period;
Percentage of patients with HbA_{1c} <7% and no body weight gain at Week 24;

- No body weight gain at Week 24 was defined as Week 24 body weight the same as or less than baseline body weight.

Percentage of patients with HbA_{1c} <7% and no weight gain at Week 24 and no experience of confirmed (PG <60 mg/dL [<3.33 mmol/L]) symptomatic hypoglycemia during the 24-week treatment period.

Safety:

Adverse events (AEs) reported by the patient or noted by the Investigator;
Standard hematology and blood chemistry.

Other:

Antidrug antibody: the status and concentration of ADA were determined at baseline, Week 4, and EOT. The samples were taken predose in the morning.

Statistical methods:

Analysis populations:

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized patients who received at least 1 dose of double-blind IMP, and had both a baseline assessment and at least 1 postbaseline assessment of any primary or secondary efficacy endpoints, irrespective of compliance with the study protocol and procedures. The safety analysis population was the randomized and treated population, defined as all randomized patients exposed to at least one dose of double-blind IMP, regardless of the amount of treatment administered.

Efficacy analyses:
The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment groups (lixisenatide or placebo), randomization strata of Week -1 HbA_{1c} (<8.0%, ≥8.0%), randomization strata of metformin use (yes, no), and country as fixed effects and baseline HbA_{1c} as a covariate. Differences between lixisenatide and placebo and its associated 2-sided 95% confidence intervals (CIs) were estimated within the framework of ANCOVA.

Similar ANCOVA model was applied on continuous secondary efficacy endpoints and Cochran-Mantel-Haenszel method stratified by randomization strata applied on categorical efficacy endpoints.

Once the primary efficacy variable was statistically significant at the 5% level (2-sided), a step-down testing procedure was to be performed to test the following secondary efficacy variables in the following prioritized order: 2-hour PPG, daily average of 7-point SMPG, body weight, total daily insulin dose, and FPG. The tests were to stop when an endpoint was found not statistically significant at the 5% level (2-sided).

Safety analyses: Safety analyses were descriptive, performed on the safety population according to treatment actually received.
Anti-lixisenatide antibodies: Data concerning ADA status and concentration were summarized using descriptive statistics.

Summary:

Population characteristics:

A total of 448 patients with T2DM were randomized to lixisenatide (n = 224) or to placebo (n = 224); 1 patient was randomized to the placebo group but did not receive treatment. Overall, 447 patients were exposed to IMP and included in the safety analyses, 446 in the mITT population (1 patient in the lixisenatide group had no post-baseline efficacy assessments). There were 18 patients (8.0%) in the lixisenatide group and 32 patients (14.3%) in the placebo group who discontinued the study treatment prematurely. The most common reasons leading to treatment discontinuation were adverse events ([AEs] 8 patients, 3.6%) in the lixisenatide group versus lack of efficacy (16 patients, 7.1%) in the placebo group.

Demographics and baseline characteristics were generally similar across the treatment groups. The median age was 55.0 years; 54.7% of the patients were female. The majority of patients were Asian (85.9%). Mean body mass index (BMI) at baseline was 27.68 kg/m², median known duration of T2DM prior to screening was 9.91 years, median duration of prior treatment with basal insulin was 1.30 years, and 88.6% of patients were using metformin at screening. Mean HbA_{1c} at screening and at Visit 9 (Week -1) before randomization were 8.63% and 8.03%, respectively, in the randomized population.

Efficacy results:

Primary efficacy endpoint was the change in HbA_{1c} from baseline to Week 24. 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 HbA1c (LS mean change of -0.62% and -0.11% in the lixisenatide and placebo groups, respectively). The LS mean difference of lixisenatide versus placebo was -0.51% (95% CI: -0.685, -0.341; p <0.0001).

At Week 24, the percentage of patients considered to be responders was higher in the lixisenatide group (37.3% for HbA1c <7% and 22.3% for HbA_{1c} ≤6.5%) than in the placebo group (13.6% for HbA_{1c} <7% and 5.9% for HbA_{1c} ≤6.5%). The percentage of patients reaching HbA_{1c} <7% at Week 24 and having no weight gain at Week 24, and the percentage of patients reaching HbA_{1c} <7% at Week 24 and having no weight gain at Week 24 nor confirmed symptomatic hypoglycemia during the on-treatment period were both higher in the lixisenatide group than in the placebo group.

For 2-hour PPG after a standardized meal, the LS mean change from baseline to Week 24 was greater in the lixisenatide group than in the placebo group; the LS mean difference between the 2 groups (-3.45 mmol/L) was statistically significant (95% CI: -4.231, -2.673; p <0.0001). The LS mean decrease from baseline to Week 24 in PG excursion after a standardized meal was also greater in the lixisenatide group than in the placebo group.

Treatment with lixisenatide showed a small improvement in terms of the average 7-point SMPG profiles compared with placebo and the LS mean difference between the 2 groups was statistically significant (-0.54 mmol/L; 95% CI: -0.870, -0.209; p = 0.0014).

The LS mean body weight change from baseline at Week 24 was greater for lixisenatide-treated patients (-1.24 kg) than for placebo-treated patients (-0.07 kg); the LS mean difference versus placebo was -1.17 kg (95% CI: -1.601, -0.736; p <0.0001).

There was a small but statistically significant difference between the lixisenatide group and the placebo group in the change in daily basal insulin dose from baseline to Week 24 (LS mean difference of lixisenatide versus placebo: -1.11 U; 95% CI: -1.856, -0.373; p = 0.0033).

A modest increase in FPG from baseline to Week 24 was observed in both treatment groups.

Safety results:

A higher percentage of patients in the lixisenatide group (63.8%) reported treatment emergent adverse events (TEAEs) during the 24-week treatment period than in the placebo group (40.8%); this imbalance was largely attributed to the higher incidences of gastrointestinal disorder TEAEs in the lixisenatide group (33.5% and 10.3% in the lixisenatide and placebo groups, respectively) and metabolism and nutrition disorders (33.5% and 21.5%, respectively).

The most commonly reported TEAE with incidence >5% difference between lixisenatide and placebo were nausea (22.8% and 5.4%, in the lixisenatide and placebo groups, respectively), hypoglycemia (25.0% and 19.7%, respectively), vomiting (11.2% and 0.9%, respectively), and decreased appetite (7.1% and 0.9%, respectively).

No patient died during the study. Thirteen patients had at least 1 serious TEAE, with a higher incidence in the lixisenatide group compared with the placebo group (11 patients [4.9%] and 2 patients [0.9%], respectively). Most serious TEAEs were not considered related to IMP. The most frequently reported serious TEAEs were from the SOCs of nervous system disorders (3 patients [1.3%] in the lixisenatide group and none in the placebo group) and gastrointestinal disorders (2 patients [0.9%] and 1 patient [0.4%], respectively). One patient in the lixisenatide group had a thyroid nodule before study and papillary thyroid cancer was confirmed by a planned biopsy during the study.

The percentage of patients with TEAEs leading to permanent treatment discontinuation was higher in the lixisenatide group than in the placebo group (8 patients [3.6%] and 4 patients [1.8%], respectively). The most common TEAEs leading to permanent treatment discontinuation were from the system organ class (SOC) gastrointestinal disorders (4 patients [1.8%] in the lixisenatide group discontinued for nausea or vomiting, and none in the placebo group); the only TEAE (by preferred term [PT]) leading to discontinuation reported by more than 2 patients was nausea in the lixisenatide group (3 patients [1.3%] in the lixisenatide group and none in the placebo group).

During the on-treatment period, 35 patients (15.6%) in the lixisenatide group and 30 patients (13.5%) in the placebo group reported at least 1 symptomatic hypoglycemic event according to protocol definition. The number of events per 100 patient-years was greater in lixisenatide group (74.5 events) than in the placebo group (48.3 events). One patient had a serious TEAE of hypoglycemia (with loss of consciousness) in the lixisenatide treatment group. This event was not classified as severe symptomatic hypoglycemia as defined per protocol since the PG value of 38 mg/dL was above the protocol defined threshold (36 mg/dL). One patient in the placebo group experienced 2 episodes of mild hypoglycemia on the day of randomization, leading to treatment discontinuation.

Two patients (0.9%) from the lixisenatide group versus none from the placebo group reported urticaria adjudicated as allergic reaction; 1 event was adjudicated as related to IMP and one event was not related to IMP. The urticaria adjudicated as related to IMP was a serious TEAE occurring on Day 11 and led to permanent treatment discontinuation. No patient in either group reported an event of confirmed increase lipase and/or amylase >2 ULN, or of pancreatitis during the study. During the on-treatment period, 2 patients (0.9%) in the lixisenatide group and 1 patient (0.4%) in the placebo group had an increase in ALT and reported the AE on the specific AE form. None of the event was serious. One patient, in the lixisenatide group, permanently discontinued treatment due to the event. During the on-treatment period, 1 patient, in the lixisenatide group, had a CV event positively adjudicated by CAC. No TEAE of increased calcitonin was reported. Symptomatic overdose was reported by 1 patient in each treatment group. One patient, in the placebo group, discontinued for pregnancy, and underwent voluntary elective abortion.

Laboratory parameters, vital sign data, and ECG findings did not reveal any specific safety concern. In the 24-week treatment period, in the lixisenatide group, 3.0% of patients were ADA-positive at baseline, 32.8% at Week 4, and 55.2% at Week 24. At Week 4, in 23 of 65 ADA-positive patients (35.4%) the antibody concentration was <LLOQ. In the other 42 patients, the antibody concentration was above LLOQ. At Week 24, in 76 of 111 ADA-positive patients (68.5%) the ADA concentration was <LLOQ. In the other 35 patients, the antibody concentration was above LLOQ. The safety profile of lixisenatide was consistent with the known safety profile of the drug. No new safety signals were identified.
Issue date: 04-Apr-2016