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Sponsor / Company: Sanofi **Drug substance(s):** AVE0010 (lixisenatide)	**Study Identifiers:** NCT01960179, UTN U1111-1134-2695 **Study code:** SFY13476
Title of the study: An open-label, multicenter 24-week and 52-week study assessing the safety and tolerability of lixisenatide in monotherapy in patients with type 2 diabetes	
Study center(s): 30 centers in Japan	
Study period: Date first patient enrolled: 16/Nov/2013 Date last patient completed: 23/Mar/2015	
Phase of development: Phase 3	
Objectives: **Primary objective** The primary objective of this study was to assess the overall safety of lixisenatide once daily (QD) treatment as monotherapy over 24 and 52 weeks in patients with type 2 diabetes mellitus (T2DM) in Japan. • To assess the effects of lixisenatide QD treatment in monotherapy over 24 and 52 weeks on: - Glycosylated hemoglobin (HbA_{1c}) reduction; - Fasting plasma glucose (FPG); - Body weight. • To assess anti-lixisenatide antibody status and concentration.	
Methodology: This was a multicenter, uncontrolled, open-label, Phase 3 study. The study comprised 4 periods: • An up to 2-week screening period; • A 6-week run-in period for patients who were previously treated with an oral antidiabetic drug (OAD) to washout any previous OADs, or patients who did not have at least 6 weeks of diet and lifestyle counseling; • A 52-week (Group 1) or 24-week (Group 2) open-label treatment period according to the treatment group; • A post-treatment follow-up period of 3 days.	
Number of patients**:**	Planned: Total 360: Group 1 (140), Group 2 (220) Randomized: Total 361: 24-week treatment period (Group 1 and Group 2): 361, 52-week treatment period (Group 1): 140 Treated: Total 361: 24-week treatment period (Group 1 and Group 2): 361, 52-week treatment period (Group 1): 140

Evaluated:

Efficacy: 361: 24-week treatment period (Group 1 and Group 2): 361, 52-week treatment period (Group 1): 140

Safety: 361: 24-week treatment period (Group 1 and Group 2): 361, 52-week treatment period (Group 1): 140

Diagnosis and criteria for inclusion: Inclusion criteria: patients with T2DM diagnosed for at least 2 months; patients not treated with antidiabetic drug or treated with a stable dose of 1 OAD for at least 3 months prior to the screening visit (except thiazolidinedione use within 6 months); and signed written informed consent. Key exclusion criteria: age at screening <20 years; HbA_{1c} <7% or >9.5% (for patients on an OAD: HbA_{1c} <6.5% or >8.5% at screening and <7% or >9.5% at the end of the run-in period); FPG >250 mg/dL (>13.9 mmol/L); use of more than 1 OAD within 3 months prior to screening; use of thiazolidinedione within 6 months prior to screening; and use of insulin within 3 months prior to screening.

Study treatments

Investigational medicinal product(s): lixisenatide

Formulation: lixisenatide was supplied as a sterile aqueous solution for subcutaneous injection in a 3-mL glass cartridge, containing 300 µg of the active ingredient (ie, 100 µg/mL), glycerol, sodium acetate trihydrate, methionine, metacresol, HCL/NaOH, and water for injection.

Route(s) of administration: subcutaneous injection using the reusable self-injector device.

Dose regimen: Each patient was to self-administered 1 injection of lixisenatide in the morning within 1 hour (ie, 0 to 60 minutes) prior to breakfast, using the specified reusable self-injector device. After baseline assessments on Day 1 (Week 0), treatment of lixisenatide started with QD injections of 10 µg for 1 week. Patients then continued with 15 µg QD injections of lixisenatide for 1 week followed by the maintenance dose of 20 µg QD injections of lixisenatide from Week 2 (Visit 4) up to the end of the treatment period, provided safety and tolerability did not prevent this dose increase. If the target dose of 20 µg was not tolerated, the dose could be decreased to 15 µg, then if necessary to 10 µg. Another attempt for a dose increase was to take place within 4 weeks. If the patient could not tolerate the target dose of 20 µg, they remained at the 15 or 10 µg dose. If the patient could not tolerate the 10 µg dose, the patient was to be discontinued from the study.

Noninvestigational medicinal product(s): Not applicable. Previous OAD (if any) had to be stopped at Visit 1.1 and was to be washed out during the run-in period of 6 weeks.

Duration of treatment: Up to 52 weeks in Group 1 and 24 weeks in Group 2.

Duration of observation:

Group 1: 60 weeks + 11 days at maximum (2 weeks screening + 6 weeks run-in for patients who stopped OAD or patients without prior diet and lifestyle counseling + 52 weeks treatment + 3 days follow-up).

Group 2: 32 weeks + 7 days at maximum (2 weeks screening + 6 weeks run-in for patients who stopped OAD or patients without prior diet and lifestyle counseling + 24 weeks treatment + 3 days follow-up).

Criteria for evaluation:

Safety endpoints (Primary): Overall safety over 24 and 52 weeks was the primary endpoint in this study and was assessed by the following: treatment-emergent adverse events (TEAEs), serious TEAEs, protocol-defined symptomatic hypoglycemia, injection site reactions, allergic reactions as assessed by the Allergic Reaction Assessment Committee (ARAC), pancreatic events, hematology parameters, serum chemistry (total bilirubin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase [ALT], alkaline phosphatase, uric acid, creatinine, glomerular filtration rate, sodium, potassium, calcium, phosphorus), lipid parameters (total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides), serum amylase and lipase, serum calcitonin, vital signs (blood pressure and heart rate), and electrocardiogram (ECG) results.

Efficacy endpoints (secondary): Efficacy variables were assessed as secondary endpoints and they were: absolute change from baseline to Week 24 and Week 52 in HbA_{1c}, FPG, and body weight; and percentage of patients at Week 24 and Week 52 with HbA_{1c} <7%, HbA1c ≤6.5%, and patients requiring rescue therapy.

Anti-lixisenatide antibodies (secondary): Anti-lixisenatide antibody status (positive and negative) and concentration was a secondary endpoint and was assessed at baseline, Week 24, Week 52 (or End of treatment) for Group 1, and at baseline and Week 24 (or End of treatment) for Group 2.

Samples for anti-lixisenatide antibody assessment were collected in the morning before the injection of the IMP at the timepoints listed above.

Statistical methods: In general, analyses of safety and efficacy variables for the 24-week treatment period were performed on the combined group of Group 1 and Group 2, and analyses for the 52-week treatment period was performed on Group 1.

Primary analysis:

Safety:

Safety analyses were performed for the safety population and are presented for each treatment period. The safety population included all patients enrolled (via the interactive web response system) and exposed to at least 1 dose of IMP, regardless of the amount of treatment administered.

The TEAEs were defined as adverse events (AEs) that developed or worsened or became serious during the on-treatment period. The on-treatment period for safety variables was defined as the time from the first dose of IMP up to 3 days after the last dose of IMP. The summaries of safety results were descriptive and presented by the 24-week and 52-week treatment periods.

Secondary analysis:

Efficacy:

Efficacy analyses were performed on the modified intent-to-treat population, defined as all enrolled patients who received at least 1 dose of open-label IMP, and had both a baseline assessment and at least 1 post-baseline assessment of any efficacy endpoints, irrespective of compliance with the study protocol and procedures. No formal statistical comparisons were performed for efficacy variables.

Efficacy variables were evaluated only by descriptive statistics using the last observation carried forward (LOCF) procedure during the 24-week and 52-week treatment periods.

Anti-lixisenatide antibodies

Anti-lixisenatide antibody status (positive, negative) at baseline, Week 24, and Week 52 is provided. Anti-lixisenatide antibody concentration was summarized using descriptive statistics by visit for patients with anti-lixisenatide antibody positive status.

Summary:

Population characteristics: A total of 361 patients were included in the analyses for the 24-week treatment period (Group 1 and Group 2 combined) and 140 patients for the 52-week treatment period (Group 1). All 361 patients were exposed to lixisenatide. Demographics and baseline characteristics were similar for patients in the 2 treatment periods. Mean age was 58.7 years in the 24-week treatment period and 58.4 years in the 52-week treatment period and the majority of patients were male (76.5% [276/361] in the 24-week treatment period and 75.0% [105/140] in the 52-week treatment period).

A total of 42/361 (11.6%) patients prematurely discontinued IMP during the 24-week treatment period and 14/140 (10.0%) during the 52-week treatment period. The main reason for permanent discontinuation of IMP was AEs (24-weeks: 35/361 [9.7%], 52-weeks: 12/140 [8.6%]).

More than 87% of patients up-titrated to 20 µg and more than 76% maintained their dose at 20 µg by the end of both treatment periods.

Efficacy results: In the 24-week treatment period, the mean HbA_{1c} (%) at baseline was 7.81% and in the 52-week treatment period it was 7.78%. Mean (95% confidence interval [CI]) HbA_{1c} (%) change from baseline was -0.94% (95% CI: -1.02 to -0.87) at Week 24 (LOCF) and -0.76% (95% CI: -0.90 to -0.61) at Week 52 (LOCF). The number (%) of patients reaching target HbA_{1c} ≤6.5% was 34.5% (124/359) at Week 24 (LOCF) and 28.1% (39/139) at Week 52 (LOCF) and reaching HbA_{1c} <7% was 62.4% (224/359) at Week 24 (LOCF) and 56.1% (78/139) at Week 52 (LOCF).

Mean (95% CI) change from baseline in FPG (mmol/L and mg/dL) was -1.02 mmol/L (95% CI: -1.15 to -0.88) (-18.34 mg/dL [95% CI: -20.79 to -15.88]) at Week 24 (LOCF) and -0.69 mmol/L (95% CI: -0.94 to -0.43) (-12.35 mg/dL [95% CI: -16.89 to -7.80]) at Week 52 (LOCF).

Mean (95% CI) change from baseline in body weight (kg) was -1.31 kg (95% CI: -1.53 to -1.09) at Week 24 (LOCF) and -1.46 kg (95% CI: -1.87 to -1.05) at Week 52 (LOCF).

Patients requiring rescue medication was minimal with only 2/140 (1.4%) patients receiving rescue therapy during the 52-week treatment period.

Safety results: Lixisenatide was well tolerated overall during both treatment periods.

During the 24-week treatment period, 268/361 (74.2%) patients reported at least 1 TEAE, including 7/361 (1.9%) patients with serious TEAEs. During the 52-week treatment period, 117/140 (83.6%) patients reported at least 1 TEAE, including 7/140 (5.0%) patients with serious TEAEs. No deaths were reported. The most frequently reported TEAE in the both treatment periods was nausea (24 weeks: 33.2% [120/361], 52-weeks: 31.4% [44/140]).

The number (%) of patients who permanently discontinued treatment due to a TEAE was 34/361 (9.4%) patients during the 24-week treatment period and 11/140 (7.9%) patients during the 52-week treatment period. The main TEAE leading to treatment discontinuation was nausea (24-weeks: 21/361 [5.8%] and 52-weeks: 5/140 [3.6%]).

The incidence of protocol-defined TEAEs of symptomatic hypoglycemia was low with 7/361 (1.9%) patients during the 24-week treatment period and 3/140 (2.1%) patients during the 52-week treatment period. One patient experienced severe symptomatic hypoglycemia (patient required the assistance of another person and either accompanied by plasma glucose <36 mg/dL [2.0 mmol/L] or associated with prompt recovery after countermeasures if no plasma glucose was available), that was reported as a serious TEAE of hypoglycemic unconsciousness (considered by the Investigator as medically important event [loss of consciousness]). The patient had skipped a meal and was consuming alcohol when he lost consciousness for approximately 5 minutes. After regaining consciousness the patient took glucose and juice and his symptoms promptly improved.

Injection site reactions were reported by 21/361 (5.8%) patients during the 24-week treatment period and by 8/140 (5.7%) patients during the 52-week treatment period. All injection site reactions were mild in intensity.

Allergic-like and allergic reactions adjudicated by the ARAC as allergic reactions were low: reported by 4/361 (1.1%) patients and 5/140 (3.6%) patients during the 24-week and 52-week treatment periods, respectively. None were adjudicated as possibly related to IMP.

No TEAEs of pancreatitis or amylase increase was reported in the study; lipase increase above 2 x upper limit of normal (ULN) were reported for 4/361 (1.1%) of patients during the 24-week treatment period. Two of these patients were in Group 1 (2/140 [1.4%]). No events were adjudicated as pancreatitis by Pancreas Safety Assessment Committee.

No events of increased calcitonin ≥20 pg/mL were reported during the study and only 1 TEAE of ALT increase was reported.

Five major cardiovascular events (3 cerebral infarctions, 1 cerebellar infarction, and 1 acute myocardial infarction) were reported in 5 patients and were all adjudicated by the Cardiovascular Events Adjudication Committee; none of the events were considered to be related to IMP by the Investigator or the Sponsor.

No clinically meaningful changes were observed in the overall safety laboratory, vital signs, and ECG results.

Anti-lixisenatide antibodies: In the 24-week treatment period, 2.2% (8/361) of patients were anti-lixisenatide antibody positive at baseline and the percentage increased with time and reached its maximum at Week 24 with 63.4% (225/355). A total of 68.4% (154/225) of patients had a concentration below the lower limit of quantification (LLOQ) at Week 24. In 31.6% (71/225) of the antibody-positive observations with concentrations above the LLOQ, the median of the antibody concentration was 13.000 nmol/L.

In the 52-week treatment period, all patients had an anti-lixisenatide antibody-negative status at baseline and the percentage of anti-lixisenatide antibody-positive patients increased to 67.6% (94/139) at Week 24 and further increased with time reaching a maximum at Week 52 with 73.4% (94/128). The anti-lixisenatide antibody concentration was below the LLOQ in 78.7% (74/94) of patients. In 21.3% (20/94) of the antibody-positive observations, the antibody concentration was above the LLOQ (median: 12.750 nmol/L) at Week 24. At Week 52, the antibody concentration was above the LLOQ in 34.0% (32/94) of the antibody-positive patients with a median of 12.900 nmol/L. Anti-lixisenatide antibody status had no impact on the efficacy or safety parameters.
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