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: Sanofi **Drug substance(s):** AVE0010 (lixisenatide)	**Study Identifiers:** UTN U1111-1129-8754, NCT01940965 **Study code:** LTS12809

Title of the study: An open-label, multicenter 52-week study assessing the safety and tolerability of lixisenatide in combination with oral anti-diabetic treatment in patients with type 2 diabetes (LTS12809)

Study center(s): 27 centers in Japan

Study period:

Date first patient enrolled: 17/Sep/2013

Date last patient completed: 21/Jul/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 in combination with background oral antidiabetic treatment over 52 weeks in patients with type 2 diabetes mellitus (T2DM) in Japan.

Secondary objectives

The secondary objectives of this study were:

- To assess the effects of lixisenatide in combination with background oral antidiabetic drugs (OADs) on:
  - Glycosylated hemoglobin (HbA_{1c});
  - Fasting plasma glucose (FPG);
  - Body weight;
  - 7-point self-measured plasma glucose (SMPG) profiles.
- To assess anti-lixisenatide antibody (baseline, Week 24, and 52).

Methodology: This was a multicenter, uncontrolled, open-label, 4-arm parallel-group study, conducted in outpatients with T2DM in Japan only. At the baseline visit, the patients were enrolled into 1 of 4 lixisenatide treatment groups according to their background OAD treatment (biguanide, thiazolidinedione [TZD], alpha-glucosidase inhibitor [alpha-GI], and glinide). The study comprised 3 periods: an up to 2-week screening period, a 52-week open-label treatment period, and a post-treatment follow-up period of 3 days.

Number of patients**:**

Number of patients	Biguanide	TZD	Alpha-GI	Glinide	Total
Planned	73	73	73	73	292
Enrolled	73	73	73	75	294
Treated	73	73	73	75	294
Evaluated efficacy	73	73	73	75	294
Evaluated safety	73	73	73	75	294

Alpha-GI = alpha-glucosidase inhibitor; TZD = thiazolidinedione.

Diagnosis and criteria for inclusion:

Key inclusion criteria: Patients with T2DM diagnosed at least 1 year before the screening visit; treated for at least 3 months prior to screening visit with 1 of following OADs at a stable dose of at least usual maintenance dose as described in the label: a biguanide (metformin hydrochloride), a TZD (pioglitazone hydrochloride), an alpha-GI (acarbose, voglibose, or miglitol), or a glinide (nateglinide, repaglinide, or mitiglinide).

Key exclusion criteria: At screening age <20 years; at screening HbA_{1c} <7% or >9.5%; at screening FPG >250 mg/dL (>13.9 mmol/L).

Study treatments

Investigational medicinal product(s): Lixisenatide

Formulation: Lixisenatide was supplied as a sterile aqueous solution for subcutaneous (SC) 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 pen-type self-injector device

Dose regimen: Lixisenatide started with QD injections of 10 μg for 1 week, and then continued with 15 μg QD for 1 week, followed by the maintenance dose of 20 μg QD up to the end of the treatment period. If the target dose of 20 μg was not tolerated, the dose of lixisenatide could be decreased to 15 μg, then if necessary to 10 μg. Another attempt for dose increase was to take place within 4 weeks. Then, if the patient could not reach or tolerate the target dose of 20 μg, he/she remained at the 15 or 10 μg dose. If the patient could not tolerate the 10 μg dose, the patient discontinued from the study. Lixisenatide was administrated in the morning within 1 hour (ie, 0 to 60 minutes) prior to breakfast.

Noninvestigational medicinal product(s): Background therapy

It was mandatory that 1 of the following OADs was used as background treatment during the study:

- Biguanide group: metformin;
- TZD group: pioglitazone;
- Alpha-GI group: acarbose, voglibose, or miglitol;
- Glinide group: nateglinide, repaglinide, or mitiglinide.

Route(s) of administration: Administered orally

Dose regimen: Patients were to continue on the background treatment they had been taking prior to the study. This was to be taken during the screening and open label treatment periods at a stable dose of at least the usual maintenance dose described in the label, unless there was a safety issue (eg, hypoglycemia). The dose was reduced at baseline for patients treated with glinides if HbA_{1c} at screening was ≥7% but <8% or could be decreased during the treatment period, in case of 2 or more symptomatic or 1 severe symptomatic hypoglycemic episodes.

Rescue therapy: Routine fasting SMPG and central laboratory alerts on FPG (and HbA_{1c} after Week 12) were set up to ensure that glycemic parameters remained under predefined thresholds values. If all the fasting SMPG values on 3 consecutive days and central laboratory alerts on FPG (and HbA_{1c} after Week 12) were above predefined thresholds, the Investigator had to ensure that no reasonable explanation existed for insufficient glucose control. If no reasons could be found or if appropriate actions failed to decrease FPG and/or HbA_{1c} below the threshold values defined for rescue therapy, rescue therapy was to be introduced in addition to the investigational medicinal product (IMP). Rescue medications could be newly initiated antidiabetic medications or background therapy given at an increased dose compared to baseline.

Duration of treatment: 52 weeks

Duration of observation: 54 weeks + 11 days at maximum (2 weeks screening + 52 weeks treatment + 3 days follow up)

Criteria for evaluation:

Safety endpoints (primary): Safety over 52 weeks was assessed by: treatment-emergent adverse events (TEAEs) and serious TEAEs, including symptomatic hypoglycemia, local tolerability at the injection site, allergic reactions as assessed by the Allergic Reaction Assessment Committee (ARAC), and pancreatitis events as assessed by the Pancreatic Safety Assessment Committee (PSAC), vital signs (blood pressure and heart rate), 12-lead electrocardiogram (ECG), hematology, serum chemistry (total bilirubin, gamma-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase [ALT], alkaline phosphatase, uric acid, creatinine, sodium, potassium, calcium, and phosphorus), lipid parameters (total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides), serum amylase and lipase, and serum calcitonin.

Efficacy endpoints (secondary): Absolute change from baseline to Week 24 in HbA_{1c}, FPG, body weight, and 7-point SMPG profiles (the average and each time point); percentage of patients with HbA_{1c} <7% or $HbA_{1c} \leq 6.5\%$ at Week 24; percentage of patients requiring rescue therapy at Week 24. Secondary endpoints were also evaluated at Week 52.

Anti-lixisenatide antibodies (secondary): Anti-lixisenatide antibody status (positive and negative) and concentration were assessed at baseline, Week 24, and Week 52/final visit. Samples for anti-lixisenatide antibody assessment were collected in the morning before the injection of the IMP at the time points listed above.

Statistical methods:

Primary analysis - Safety: All safety analyses were performed on the safety population, which was defined as all patients enrolled (via the interactive web response system) and exposed to at least 1 dose of the IMP, regardless of the amount of treatment administered. Treatment emergent adverse events were defined as adverse events (AEs) that developed or worsened (according to the Investigator's opinion) 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 provided for the on-treatment period by background OAD group and in addition for the overall safety population for the analyses of AEs, using descriptive statistics.

Secondary analysis - Efficacy: All efficacy analyses were performed on the modified intent-to-treat (mITT) population, corresponding to all enrolled patients who received at least 1 dose of the 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. The summaries of efficacy data were provided by background OAD group. Descriptive statistics were provided for all continuous variables at the scheduled visits and change from baseline at each visit point; at Weeks 24 and 52, analyses using the Last Observation Carried Forward (LOCF) procedure were also provided. Categorical analyses were performed on HbA_{1c} levels (percentage of patients with HbA_{1c} <7% and $\leq 6.5\%$ at Week 24 and Week 52). The percentage of patients requiring rescue therapy at Week 24 and Week 52 was also provided.

Secondary analysis - Anti-lixisenatide antibodies: Anti-lixisenatide antibody status (positive, negative) at baseline, at Weeks 24 and 52, at the time point "prior to rescue", and at the last on-treatment measurement were provided. Anti-lixisenatide antibody concentration was summarized using descriptive statistics. Summaries were provided by background OAD group and for the overall safety population.

Summary:

Population characteristics: A total of 294 patients were enrolled to 1 of the 4 background OAD groups: 73 patients in each of the Biguanide, TZD, and Alpha-GI groups, and 75 patients in the Glinide group. All patients were treated with the IMP.
During the 52-week study treatment period, the percentage of patients who discontinued treatment with the IMP in the different groups was 4.1% (3/73 patients) in the Biguanide group, 17.8% (13/73) in the TZD group, 12.3% (9/73) in the Alpha-GI group and 16.0% (12/75) in Glinide group. The main reason for treatment discontinuation was AEs in each of the background OAD groups.
The demographic and baseline characteristics for the safety population were generally similar across all background OAD groups.
Regarding the IMP dosing across the 4 background OAD groups, 84.0% (63/75) to 90.4% (66/73) of the patients were receiving the maintenance dose of 20 μg lixisenatide QD at the end of the titration period, and 78.1% (57/73) to 93.2% (68/73) maintained their dose at 20 μg by the end of treatment.

Safety results: Overall, lixisenatide was well tolerated over 52 weeks of treatment in patients with T2DM treated with either biguanide, TZD, alpha-GI, or glinide as background therapy. The safety profile of lixisenatide over 52 weeks of treatment was generally similar across the 4 background OAD groups and consistent with the known safety profile of the glucagon-like peptide 1 (GLP-1) receptor agonist class.

The percentage of patients who experienced TEAEs during the 52-week treatment period ranged between 83.6% (61/73; TZD and Alpha-GI groups) and 90.4% (66/73; Biguanide group) across the 4 background OAD groups. Nausea was the most frequently reported TEAE in the TZD, Alpha-GI, and Glinide groups (40.0% to 45.2% of patients) and the second most frequently reported in the Biguanide group (31.5%). TEAEs related to lixisenatide that were reported most frequently across the 4 background OAD groups were nausea, constipation, vomiting, and hypoglycemia.

A total of 8 patients reported serious TEAEs: 3/73 (4.1%) patients in the Biguanide group, 2/73 (2.7%) in the TZD group, 0 in the Alpha-GI group, and 3/75 (4.0%) in the Glinide group; no serious TEAEs were considered as related to the IMP or the noninvestigational medicinal product (NIMP). One fatal TEAE of gastric cancer was reported in the TZD group.

The percentage of patients with TEAEs leading to permanent discontinuation of treatment with the IMP was 4.1% (3/73 patients) in the Biguanide group, 13.7% (10/73) in the TZD group, 11.0% (8/73) in the Alpha-GI group, and 12.0% (9/75) in the Glinide group. Nausea was the most frequently reported TEAE leading to discontinuation in all background OAD groups, apart from the Biguanide group: 0 patients in the Biguanide group, 11.0% (8/73) of patients in the TZD group, 6.8% (5/73) in the Alpha-GI group, and 5.3% (4/75) in the Glinide group. The events of nausea leading to discontinuation were mild or moderate in intensity.

Symptomatic hypoglycemia (as defined per protocol) during the on-treatment period was reported in 4/73 (5.5%) patients in the Biguanide group, 1/73 (1.4%) in the Alpha-GI group, and 8/75 (10.7%) in the Glinide group. No patients reported symptomatic hypoglycemia in the TZD group. There were no patients with severe symptomatic hypoglycemia.

The percentage of patients with injection site reactions during the on-treatment period was 9.6% (7/73 patients) in the Biguanide group, 6.8% (5/73) in the TZD group, 4.1% (3/73) in the Alpha-GI group, and 1.3% (1/75) in the Glinide group. All injection site reactions reported during the study were mild in intensity and none was serious. One TEAE of injection site erythema in the TZD group led to discontinuation of treatment with the IMP.

The percentage of patients with allergic reactions during the on-treatment period as adjudicated by the ARAC was low: 5.5% (4/73) in the Biguanide group, 1.4% (1/73) in the TZD group, 1.4% (1/73) in the Alpha-GI group, and 0 in the Glinide group. None of these allergic reactions were considered as possibly related to the IMP by the ARAC.

No events were adjudicated as pancreatitis by the PSAC and no events of pancreatic neoplasms were reported in the study. One patient in the Biguanide group had 2 events which were adjudicated as major cardiovascular events by the Cardiovascular Events Adjudication Committee: a post-treatment AE of basal ganglia infarction and a post-treatment AE of cerebral artery occlusion. Both events were considered as not related to the IMP. No patients had events reported by the Investigators as increased calcitonin ≥20 pg/mL or increase in ALT during the study.

One symptomatic overdose with abdominal distension considered as related to the IMP by the Investigator was reported in the Glinide group.

Regarding laboratory parameters, there were generally no clinically meaningful changes from baseline to the end of treatment observed in any of the background OAD groups. Generally, few patients had post-baseline PCSAs or out of normal range values for the different laboratory parameters.

A small decrease from baseline to end of treatment was observed in all background OAD groups for systolic and diastolic pressure and no clinically meaningful changes in heart rate were observed. Few patients had PCSAs for vital signs during the on treatment period.

Efficacy results: The mean change (95% confidence interval [CI]) from baseline in HbA_{1c} at Weeks 24 and 52 was -0.98% (95% CI: -1.15 to -0.81) and -0.80% (95% CI: -0.99 to -0.61), -1.03% (95% CI: -1.18 to -0.88) and -1.02% (95% CI: -1.18 to -0.85), -1.22% (95% CI: -1.38 to -1.07) and -1.08% (95% CI: -1.26 to -0.90), and -1.17% (95% CI: -1.34 to -0.99) and -0.99% (95% CI: -1.17 to -0.80) in the Biguanide, TZD, Alpha-GI, and Glinide groups, respectively.

The percentage of patients with HbA_{1c} <7.0% at Weeks 24 and 52 was, respectively, 55.7% (39/70) and 41.2% (28/68) in the Biguanide group, 64.1% (41/64) and 55.0% (33/60) in the TZD group, 70.8% (46/65) and 59.4% (38/64) in the Alpha-GI group, and 51.5% (34/66) and 44.3% (27/61) in the Glinide group. Additionally, 25.8% (17/66) to 43.1% (28/65) and 21.3% (13/61) to 37.5% (24/64) of patients across the 4 groups reached HbA_{1c} ≤6.5% at Weeks 24 and 52, respectively.

The mean (95% CI) change in FPG from baseline at Week 24 was -1.16 mmol/L (95% CI: -1.52 to -0.80) (-20.91 mg/dL [95% CI: -27.36 to -14.47]) in the Biguanide group, -0.74 mmol/L (95% CI: -1.01 to -0.48) (-13.37 mg/dL [95% CI: -18.13 to -8.60]) in the TZD group, -1.10 mmol/L (95% CI: -1.46 to -0.74) (-19.83 mg/dL [95% CI: -26.38 to -13.28]) in the Alpha-GI group, and -1.04 mmol/L (95% CI: -1.36 to -0.72) (-18.70 mg/dL [95% CI: -24.51 to -12.89]) in the Glinide group.

The mean (95% CI) change in FPG from baseline at Week 52 was -0.73 mmol/L (95% CI: -1.07 to -0.38) (-13.10 mg/dL [95% CI: -19.28 to -6.92]) in the Biguanide group, -0.92 mmol/L (95% CI: -1.20 to -0.64) (-16.58 mg/dL [95% CI: -21.67 to -11.50]) in the TZD group, -1.11 mmol/L (95% CI: -1.54 to -0.68) (-19.97 mg/dL [95% CI: -27.66 to -12.28]) in the Alpha-GI group, and -0.86 mmol/L (95% CI: -1.25 to -0.46) (-15.41 mg/dL [95% CI: -22.58 to -8.24]) in the Glinide group.

The mean change in body weight from baseline at Week 24 and 52, respectively, was -1.63 kg (95% CI: -2.15 to -1.11) and -1.62 kg (95% CI: -2.17 to -1.06) in the Biguanide group, -1.86 kg (95% CI: -2.34 to -1.38) and -1.95 kg (95% CI: -2.60 to -1.29) in the Alpha-GI group, as well as -0.60 kg (95% CI: -1.19 to -0.00) and -1.10 kg (95% CI: -1.93 to -0.28) in the TZD group, and -0.79 kg (95% CI: -1.35 to -0.23) and -0.88 kg (95% CI: -1.53 to -0.22) in the Glinide group.

Average 7-point SMPG decreased from baseline at Weeks 24 and 52 and the mean changes were similar across all background OAD groups. In all groups, the greatest decreases were observed at 2 hours post-breakfast and 2 hours post-lunch.

Five patients in total required rescue therapy during the on-treatment period.

Anti-lixisenatide antibody results: At baseline, 6/293 (2.0%) patients were already positive for anti-lixisenatide antibody: 1/73 (1.4%) patient in the Biguanide group, 0 in the TZD group, 4/72 (5.6%) in the Alpha-GI group, and 1/75 (1.3%) in the Glinide group. The percentage of anti-lixisenatide antibody-positive patients increased with time. It was 63.1% (183/290) in the overall safety population at Week 24, ranging between 52.1% (38/73) and 68.5% (50/73) across the 4 background OAD groups, and reached its maximum at Week 52 with overall 78.9% (206/261) of patients, ranging between 73.1% (49/67) and 85.7% (60/70) of patients across the 4 background OAD groups.
Anti-lixisenatide antibody status had no clinically relevant impact on safety endpoints or on the analyses of HbA_{1c}. At Week 24, the mean change in HbA_{1c} from baseline ranged between -0.98% and -1.23% in patients with positive anti-lixisenatide antibody status and between -1.04% and -1.21% in patients with negative anti-lixisenatide antibody status across the Biguanide, TZD, and Alpha-GI groups. In the Glinide group, the mean change in HbA_{1c} from baseline at Week 24 was -1.05% (95% CI: -1.25 to -0.86) for patients with positive and -1.46% (95% CI: -1.81 to -1.11) for patients with negative anti-lixisenatide antibody status.

Issue date: 10-Jun-2016