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Sponsor / Company: Sanofi **Drug substance(s):** AVE0010 (lixisenatide)	**Study Identifiers:** NCT01768559, UTN U1111-1131-4936, EudraCT 2012-004096-38 **Study code:** EFC12626
Title of the study: A randomized, open-label, active-controlled, 3-arm parallel-group, 26-week study comparing the efficacy and safety of lixisenatide to that of insulin glulisine once daily and insulin glulisine three times daily in patients with Type 2 diabetes insufficiently controlled with insulin glargine with or without metformin	
Study center(s): 199 active centers across 18 countries (Canada, Chile, Czech Republic, Estonia, France, Germany, Hungary, Italy, Latvia, Lithuania, Mexico, Poland, Romania, Russia, Spain, Ukraine, United Kingdom, United States).	
Study period: Date first patient enrolled: 08/Jan/2013 Date last patient completed: 03/Dec/2014	
Phase of development: Phase 3	

Objectives:

Primary objective

To demonstrate in type 2 diabetic patients (T2DM) not adequately controlled on insulin glargine alone or with metformin:

The non-inferiority of lixisenatide versus insulin glulisine once daily (QD) (Basal Plus regimen) on glycated hemoglobin HbA_{1c} reduction at Week 26.

The non-inferiority of lixisenatide versus insulin glulisine three times daily (TID) (Basal Bolus regimen) on HbA_{1c} reduction or superiority on body weight change at Week 26.

Secondary objectives

To assess the effect of the 3 treatments/regimens when used in combination with insulin glargine alone or with metformin:

At Week 26 on:

The percentage of patients who reached the target of HbA_{1c} <7% or ≤6.5% at Week 26

Body weight

Fasting plasma glucose (FPG)

Post-prandial glucose (PPG) and glucose excursions during standardized meal test (patients having an injection of investigational medicinal product [IMP] before breakfast)

Seven-point self-monitored plasma glucose (SMPG) profile (mean daily value and each time point)

Daily insulin(s) doses

On the percentage of patients who:

Reached the target of HbA_{1c} <7% at Week 26 and did not experience documented (plasma glucose [PG] <60 mg/dL) symptomatic hypoglycemia during the 26-week treatment period.

Reached the target of HbA_{1c} <7% and had no weight gain at Week 26.

Reached the target of HbA_{1c} <7%, had no weight gain at Week 26 and did not experience documented (PG <60 mg/dL) symptomatic hypoglycemia during the 26-week treatment period.

To assess safety and tolerability of the 3 treatments/regimens when used in combination with insulin glargine alone or with metformin in particular on:

Documented (PG <60 mg/dl) symptomatic hypoglycemia (number of patients with at least one episode and number of events per patient-year), severe hypoglycemia.

Adverse events (AEs), serious adverse events, vital signs, safety laboratory values.

Methodology: Open-label, 1:1:1 randomized, active-controlled, 3-arm, parallel-group multicenter study comparing:

Insulin glargine ± metformin + lixisenatide QD (lixisenatide regimen)

Insulin glargine ± metformin + insulin glulisine QD (Basal Plus regimen)

Insulin glargine ± metformin + insulin glulisine TID (Basal Bolus regimen)

Randomization was stratified:

By Visit 7 (Week -1) stratum of HbA_{1c} (<8%, ≥8%)

By randomization stratum of metformin use (yes, no)

Number of patients**:** Planned: 855

Randomized: 894

Treated: 893

Evaluated:

Efficacy: 890

Safety: 893

Diagnosis and criteria for inclusion: Patients with T2DM diagnosed for at least 1 year, treated with basal insulin (for at least 6 months, with a stable regimen for at least 3 months and a stable ≥20 U/day dose for at least 2 months prior to Visit 1) alone or in combination with 1 to 3 oral anti-diabetic drugs (OADs), that could be metformin (≥1.5g/day or maximal tolerated dose), a sulfonylurea (SU), a dipeptidyl-peptidase-4 (DPP-4) inhibitor, a glinide (all at a stable dose for at least 3 months prior to Visit 1).

Study treatments

Investigational medicinal product(s): lixisenatide, insulin glulisine

Formulation: Lixisenatide was supplied as disposable pre-filled pen (lixisenatide pen) containing 3 mL of a sterile aqueous solution for subcutaneous (SC) injection with 150 µg (for the 10 µg initiation dose) or 300 µg (for the 20 µg maintenance dose) of the active ingredient (ie, 50 or 100 µg/mL), glycerol, sodium acetate trihydrate, methionine, metacresol, hydrochloric acid/sodium hydroxide, water for injection.

Insulin glulisine 100 units/mL solution was supplied as Apidra® SoloSTAR® pre-filled pen containing 3 mL of solution for SC injection, equivalent to 300 units of the active ingredient, metacresol, sodium chloride, trometamol, polysorbate 20, hydrochloric acid/sodium hydroxide, water for injection.

Route(s) of administration: Subcutaneous (SC)

Dose regimen: For lixisenatide, an initiation dose of 10 µg was administered for the first 14 days of treatment, and then the maintenance dose of 20 µg was used.

For insulin glulisine, the starting dose was 3 to 5 U, once daily in the Basal Plus arm and for each meal in the Basal Bolus arm. The dose was then titrated to obtain before the next meal or at bedtime an SMPG value >5.6 mmol/L (100 mg/dL) and ≤7.8 mmol/L (140 mg/dL) while avoiding hypoglycemia.

Noninvestigational medicinal product: insulin glargine

Formulation: Insulin glargine was supplied as disposable Lantus® SoloSTAR® self-injector prefilled pen containing 300 units of insulin glargine.

Route(s) of administration: SC

Dose regimen: The starting dose of insulin glargine was based on pre-study basal insulin dose levels of patients. The insulin doses were then titrated to reach the target SMPG in the range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL) without recurrent or severe hypoglycemia. After reaching the target range, the insulin doses were adjusted depending on the prevailing plasma glucose to maintain the glycemic control over the remaining study duration.

Duration of treatment: 26 weeks

Duration of observation: up to 41 weeks

Criteria for evaluation:

Efficacy:

Primary endpoints

Change in HbA_{1c} from baseline to Week 26

Change in body weight from baseline to Week 26 (lixisenatide versus insulin glulisine TID)

Secondary endpoints

Percentage of patients reaching HbA_{1c} <7% at Week 26

Percentage of patients reaching HbA_{1c} ≤6.5% at Week 26

Change in body weight from baseline to Week 26 (lixisenatide versus insulin glulisine QD)

Percentage of patients with no weight gain

Change in FPG from baseline to Week 26.

Change from baseline to Week 26 in post-prandial glucose and glucose excursions (30-minute, 1-hour, and 2-hour post-prandial) during a standardized meal test (in patients having an injection of IMP before breakfast)

Change in 7-point SMPG profiles from baseline to Week 26 (each time point and mean daily value)

Change in insulin glargine dose from baseline to Week 26

Insulin glulisine dose and total insulin dose at Week 26

The percentage of patients who:

Reached the target of HbA_{1c} <7% at Week 26 and did not experience documented (<3.3 mmol/L [PG <60 mg/dL]) symptomatic hypoglycemia during the 26-week treatment period.

Reached the target of HbA_{1c} <7% and had no weight gain at Week 26.

Reached the target of HbA_{1c} <7%, had no weight gain at Week 26, and did not experience documented (<3.3 mmol/L [PG <60 mg/dL]) symptomatic hypoglycemia during the 26-week treatment period.

Safety: Adverse events reported by the patient/subject or noted by the Investigator. Standard hematology and serum chemistry.

Statistical methods:

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

Primary analysis

The primary analysis was based on a co-primary endpoint in patients with insulin glargine ± metformin:

Non-inferiority of lixisenatide versus Basal Plus on HbA_{1c} change from baseline to Week 26.

2a. Non-inferiority of lixisenatide versus Basal Bolus on HbA_{1c} change from baseline to Week 26.

2b. Superiority of lixisenatide versus Basal Bolus on body weight change from baseline to Week 26.

The study was to be declared positive if both 1 and 2 (at least one of 2a or 2b) were met.

Overall, the statistical assessment was done at α=0.025 (1-sided) for the primary composite endpoint. Both 1 and 2 (either 2a or 2b) were assessed separately at α=0.025 (1-sided), and both 1 and 2a were assessed at a non-inferiority margin of 0.4%.

For the co-primary endpoint 1, the non-inferiority was assessed using the upper bound of the 2-sided 95% CI. If the upper bound of the 95% CI was less than 0.4%, the non-inferiority of lixisenatide versus Basal Plus was to be claimed. If the non-inferiority was met, then the superiority over Basal Plus was to be checked.

For the co-primary endpoint 2 (2a and 2b), Hochberg procedure was used to for these 2 comparisons at α=0.025 (1-sided) in order to control the type 1 error. The Hochberg process worked as follows: if non-inferiority of lixisenatide versus insulin glulisine TID on HbA_{1c} and superiority of lixisenatide versus insulin glulisine TID on body weight were both met at α=0.025 (1-sided), then endpoint 2 was met at α=0.025 (1-sided). If only one of them was met, then the one met should be tested at α=0.0125 (1-sided). The non-inferiority on HbA_{1c} was assessed using the upper bound of the 2-sided 95% CI (or 97.5% CI). If the upper bound of the 95% CI (or 97.5% CI) on HbA_{1c} was less than 0.4%, the non-inferiority of lixisenatide versus insulin glulisine TID on HbA_{1c} was met at 1-sided α=0.025 (or α=0.0125). The superiority on body weight was assessed by comparing the p-value with the 1-sided α=0.025 (or α=0.0125).

If 2a (non-inferiority in HbA_{1c} versus basal bolus) was met, then the superiority over basal bolus on HbA_{1c} change from baseline to Week 26 was to be checked.

The primary endpoints were analyzed using an analysis of covariance (ANCOVA) model with treatment (lixisenatide, insulin glulisine QD, and insulin glulisine TID), Visit 7 (Week -1) stratum of HbA_{1c} (<8%, ≥8%), randomization stratum of metformin use (yes, no) and country as fixed effects and using the corresponding baseline value as a covariate. The baseline value was defined as the last available value prior to the first dose administration of study treatment. Difference between lixisenatide and insulin glulisine QD and the associated 2-sided 95% CI was estimated within the framework of the above ANCOVA model for HbA_{1c}. Similarly, difference between lixisenatide and insulin glulisine TID and the associated 2-sided 95% CI (and 97.5% CI if either 2a or 2b was not met) was estimated for HbA_{1c} and body weight.

Analysis of secondary endpoints

All categorical secondary efficacy endpoints were analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified by stratum of HbA_{1c} at Visit 7 (Week -1) (<8, ≥8 %) and randomization stratum of metformin use (yes, no).

For HbA_{1c} responders (<7%, ≤6.5%), summary tables and graphs were provided by treatment group at scheduled visits (using OC) and at Week 26 (using last observation carried forward [LOCF]). A sensitivity analysis was performed excluding patients whose HbA_{1c} values at baseline were <7% (for the 7% responder analysis) or ≤6.5% (for the ≤6.5% responder analysis). The summary by visit was also provided excluding those patients.

All continuous secondary efficacy endpoints except for insulin glulisine and total daily insulin dose, were analyzed using the same primary ANCOVA model. The missing data at Week 26 were imputed using the LOCF approach. This model included fixed effect terms for treatment group (lixisenatide, insulin glulisine QD, and insulin glulisine TID), stratum of HbA_{1c} at Visit 7 (Week 1) (<8%, ≥8 %), randomization stratum of metformin use (yes, no), and country, with the corresponding baseline value used as a covariate. For secondary endpoints, no control of type 1 error was made (ie, no multiplicity adjustment for secondary endpoints).

Safety analyses

Safety analyses for the 26-week open-label treatment period were descriptive.

Summary:

Population characteristics:

A total of 894 patients were randomized, 298 in each treatment group. Demographic and baseline characteristics were generally similar across the treatment groups. The study population was primarily Caucasian (92.6%).The median age at screening of the randomized population was 60.0 years and 41 (4.6%) patients were ≥75 years of age. 54.7% of the patients were female. The majority of the population was either obese or overweight with a median BMI at baseline for the randomized population of 31.9 kg/m^2.

Efficacy results:

Co-primary endpoints 1, 2a and 2b were all met: when added to insulin glargine, lixisenatide was non-inferior to insulin glulisine QD and non-inferior to insulin glulisine TID for HbA_{1c} change from baseline to Week 26, and superior to insulin glulisine TID for body weight change from baseline to Week 26. In addition, body weight reduction was also greater with lixisenatide than with insulin glulisine QD.

After a 12-week titration of insulin glargine which led to a decrease in HbA1c from 8.50% to 7.76%:

Mean changes in HbA_{1c} from baseline to Week 26 were -0.63% in the lixisenatide group, -0.58% in the insulin glulisine QD group, and -0.84% in the insulin glulisine TID group reaching 7.17%, 7.21% and 6.96%, respectively.

Mean changes in body weight from baseline to Week 26 were -0.63 kg in the lixisenatide group, 1.03 kg in the insulin glulisine QD group and 1.37 kg in the insulin glulisine TID group.

Daily dose of insulin glargine increased from 40 to 66 U during the 12-week titration, and did not change much throughout the study treatment period in the 3 treatment groups. Fasting plasma glucose values substantially decreased during the titration period and remained stable during the study treatment period and comparable in all 3 groups. At the end of the 26-week treatment period, insulin glulisine daily dose was raised up to approximately 10 U in the QD group and 20 U in the TID group. Postprandial glycemic control as measured by 2-hour PPG during liquid meal test was improved in all 3 groups with a difference in favor of lixisenatide as compared to both glulisine groups (LS mean change from baseline to Week 26 in 2-hour PPG was -3.64 mmol/L [-65.50 mg/dL] with lixisenatide, -1.57 mmol/L [-28.25 mg/dL] with insulin glulisine QD and -1.41 [-25.35 mg/dL] with insulin glulisine TID).

The rate of responders achieving a glycemic target of HbA_{1c} <7% at Week 26 was 42.1% with lixisenatide, 38.4% with insulin glulisine QD and 49.2% with insulin glulisine TID. The percentage of patients reaching HbA_{1c} <7% at Week 26 without documented symptomatic hypoglycemia (plasma glucose <3.3 mmol/L [60 mg/dL]) was 29.4%, 24.2% and 26.1% in the lixisenatide, insulin glulisine QD and insulin glulisine TID groups, respectively. The percentage of patients reaching HbA_{1c} <7% with no weight gain at Week 26 was higher in the lixisenatide group than in the 2 other treatment groups: 31.2% versus 16.7% in the insulin glulisine QD group and 17.6% in the insulin glulisine TID group. The rate of responders achieving a glycemic target of HbA_{1c} <7%, with no weight gain and without documented hypoglycemia was at least twice higher with lixisenatide (22.2%) than with insulin glulisine QD (9.2%) or TID (10.8%).

Safety results:

The cumulative duration of treatment exposure was similar in the lixisenatide, insulin glulisine QD and insulin glulisine TID groups: 142.2, 145.9 and 143.8 patient years, respectively.

At the end of the treatment period, most patients, 83.2%, were receiving 20 µg of lixisenatide QD in the lixisenatide group, which was the target and maximal dose allowed by the study.

The percentages of patients with any TEAEs were 74.2% in the lixisenatide group, 73.8% in the insulin glulisine QD group and 80.3% in the insulin glulisine TID group. More patients receiving lixisenatide experienced nausea and vomiting symptoms than in the insulin glulisine groups (at the HLT level: 26.5% versus 3.0% in the insulin glulisine QD group and 2.4% in the insulin glulisine TID group) and more patients taking insulin glulisine experienced symptomatic hypoglycemia as reported by Investigator than in the lixisenatide group (35.9% in the lixisenatide group versus 46.5% and 52.4% in the glulisine QD and TID groups, respectively). Accidental overdose with the IMP were reported in the glulisine groups (4.3% of patients in glulisine QD and 6.8% in glulisine TID group) and not reported with lixisenatide.

Deaths were reported in 1 patient in the lixisenatide group and 2 patients in the insulin glulisine TID group. In addition, 1 patient died during the run-in period.

The incidence of serious TEAEs was 3.7%, 3.7%, and 4.8% in the lixisenatide, insulin glulisine QD and insulin glulisine TID groups, respectively.

The percentage of patients who had TEAEs leading to treatment discontinuation was higher in the lixisenatide group than in the insulin glulisine QD and TID groups (5.0% versus 0.7% and 1.0%, respectively), largely due to the higher frequency of gastrointestinal disorders in the lixisenatide group (3.7% in the lixisenatide group versus none in the other groups), including nausea and vomiting (1.3% each).

Consistent with the known safety profile of lixisenatide, nausea and vomiting was more frequently reported by patients in the lixisenatide group than in the 2 other groups. Nausea was reported in 25.2% of patients in the lixisenatide group versus 1.7% and 1.0% of patients in the insulin glulisine QD and TID groups, respectively. Vomiting was reported in 8.7%, 1.7% and 2.0% of patients, respectively. Of patients who reported nausea and/or vomiting, most continued treatment and completed the study.

The rate of symptomatic hypoglycemia as reported by Investigator was significantly lower with lixisenatide than with both insulin glulisine regimens (estimated rate ratio versus insulin glulisine QD of 0.64; 95% CI: 0.45 to 0.89 and versus insulin glulisine TID of 0.49; 95% CI: 0.36 to 0.69). Symptomatic hypoglycemia as reported by Investigator led to treatment discontinuation in 1 patient in the lixisenatide group. Symptomatic hypoglycemia was reported as serious TEAE in 3 patients, all in the glulisine QD group; of these, 2 patients reported severe hypoglycemia associated with unconsciousness. Symptomatic hypoglycemia, as defined per protocol (ie, with an accompanying plasma glucose <3.3 mmol/L [60 mg/dL] or associated with prompt recovery after countermeasures if no plasma glucose measurement was available) was also reported less frequently with lixisenatide (32.9% of patients) than with insulin glulisine QD (38.9%) or TID (44.9%).

Allergic reactions as adjudicated by the Allergic Reaction Assessment Committee (ARAC) were reported in 3 (1.0%) patients in the lixisenatide group and 1 (0.3%) patient in the insulin glulisine TID group during the on-treatment period. None of the events (urticaria and allergic rhinitis) was serious and none was considered as possibly related to IMP.

Injection site reactions were reported in 4 (1.3%) patients in the lixisenatide group and 1 (0.3%) patient in each insulin glulisine group during the on-treatment period. All were of mild intensity and none led to permanent treatment discontinuation.

Suspected pancreatitis was reported in 1 lixisenatide-treated patient. The event resolved within four days. Lixisenatide was reintroduced and the patient completed the study as planned. The event was positively adjudicated as acute pancreatitis by the Pancreatic Safety Assessment Committee (PSAC).

Malignant pancreatic neoplasm was reported in 1 lixisenatide-treated patient versus none in the other groups. The patient was diagnosed with metastatic pancreatic cancer 35 days after the first administration of lixisenatide and died 17 days later. The event was positively adjudicated and considered as not related to lixisenatide by the PSAC.

Cardiovascular events as adjudicated by the Cardiovascular events Adjudication Committee (CAC) were reported in 2 patients in the lixisenatide group versus 1 in the insulin glulisine QD group and 4 in the insulin glulisine TID group.

Treatment-emergent AEs related to increased calcitonin levels and TEAEs related to ALT increase were reported in a low and similar percentage of patients in each treatment group.

Laboratory parameters, vital sign data, and electrocardiogram (ECG) readings did not reveal any specific safety concerns. The safety profile of lixisenatide and insulin glulisine was consistent with the known safety profile of these drugs. No new safety signals were identified with lixisenatide.
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