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Sponsor: Sanofi **Drug substance(s):** AVE0010 (lixisenatide)	**Study Identifiers:** UTN U1111-1159-5323, NCT02200991 **Study code:** LIXISL06651
Title of the study: A randomized, multicenter, open-label, parallel-group, 28 days phase IV study comparing the PPG profile of lixisenatide with that of sitagliptin add on to insulin glargine in type 2 diabetes mellitus	
Study center(s): 15 centers in Japan	
Study period: Date first patient enrolled: 08/Aug/2014 (first signed written informed consent) Date last patient completed: 02/Nov/2015	
Phase of development: Phase 4	

Objectives:

Primary Objective - To compare postprandial plasma glucose (PPG) reduction and blood glucose profile of lixisenatide with those of sitagliptin in combination with insulin glargine.

Secondary Objectives:

- To assess the effects of lixisenatide as compared to sitagliptin on:
  - Maximum PPG excursion;
  - Changes in blood C-peptide and glucagon concentrations following a standardized breakfast;
  - Changes in fasting blood 1.5-anhydro-D-glucitol (1.5-AG) and glycoalbumin concentrations.
- To assess gastric emptying rate;
- To assess safety and tolerability.

Methodology: This was a randomized, multicenter, open-label, parallel-group, 28 days phase intravenous IV study in Japanese patients with type 2 diabetes mellitus. The study comprised 3 periods: a 2-week screening period, a 4-week (28-day) open-label treatment period, and a 3-day follow-up period. Patients with type 2 diabetes mellitus were randomized in a 1:1 ratio to receive either lixisenatide or sitagliptin on top of insulin glargine. The randomization was stratified by sulfonylurea (SU) use at screening (yes, no). Lixisenatide was started with once-daily injection of 10 µg, then increased weekly by 5 µg up to once-daily injection of 20 µg. Sitagliptin was administered as once-daily oral dose of 50-mg tablet.

Number of patients**:** Planned: 148 (74 in each treatment group)

40 for gastric emptying rate test (20 in each treatment group)

Randomized: 136 (lixisenatide: 69, sitagliptin: 67)

Treated: 136 (lixisenatide: 69, sitagliptin: 67)

Evaluated:

Efficacy: 135 (lixisenatide: 69, sitagliptin: 66)

Safety: Safety: 136 (lixisenatide: 69, sitagliptin: 67)

Pharmacodynamics (PD) (for the evaluation of gastric emptying rate):

43 (lixisenatide: 20, sitagliptin: 23)

Diagnosis and criteria for inclusion:

- Patients with type 2 diabetes mellitus diagnosed for at least 5 years before screening visit.
- Patients treated for at least 3 months prior to screening visit with one of the following treatments:
  - Insulin glargine at stable dose;
  - Insulin glargine at stable dose and SU without dose change.
- At screening: Hemoglobin A1c (HbA1c) ≥7.0% and ≤10.0%;
- At screening: Fasting plasma glucose (FPG) ≤180 mg/dL;
- At written informed consent: age ≥20 and ≤75 years;
- Signed written informed consent.

Study treatments

Investigational medicinal product(s):

Lixisenatide (tested drug)

Sitagliptin phosphate hydrate formulation (sitagliptin) (control drug)

Formulation:

Lixisenatide: 3-mL aqueous solution

Sitagliptin: 50-mg tablet

Route(s) of administration:

Lixisenatide: Subcutaneous injection

Sitagliptin: Oral administration

Dose regimen:

Lixisenatide: Once-daily, 30 minutes prior to breakfast

Lixisenatide was started with once-daily injection of 10 µg, then increased weekly by 5 µg up to once-daily injection of 20 µg

Sitagliptin: 50 mg once-daily, 30 minutes prior to breakfast

Noninvestigational medicinal product(s): Insulin Glargine (Genetical Recombination) injection solution (LANTUS® Inj. SoloStar®)

Formulation: 3-mL aqueous solution

Route(s) of administration: Subcutaneous injection

Dose regimen: Subcutaneous injection once-daily before breakfast or at bedtime.

Patients treated for at least 3 months prior to screening visit with insulin glargine at stable dose ±SU were included.

For patients with screening HbA1c value ≤7.5%, the dose of insulin glargine had to be reduced by 20% at Visit 2. In case FPG could not be controlled after reduced dose, insulin glargine could be increased up to the dose received at screening.

In addition, for those treated with SU and with screening HbA1c value <8%, it was recommended per protocol to decrease by at least 25% the SU dose (or could be stopped if the lowest dose of SU was used) at Visit 2.

Through the study period, basically the same dose and timing of administration of insulin glargine was to be maintained. However, the dose of insulin glargine could be adjusted depending on occurrence or increase risk of hypoglycemia.

Duration of treatment: 28 days

Duration of observation: Up to 7 weeks (screening period: 2 weeks, treatment period: 4 weeks, follow-up period: 3 days)

Criteria for evaluation:

Efficacy:

Primary endpoint:

Change in PPG ($AUC_{0:00-4:00h}$*) after a standardized breakfast from baseline to Day 29.

*$AUC_{0:00-4:00h}$: AUC of the blood glucose concentrations from the time of standardized breakfast start (0 hour) to 4 hours after the breakfast.

Secondary endpoints:

Changes in the following variables from baseline to Day 29:

- Maximum PPG excursion;
- C-peptide and glucagon levels after standardized breakfast;
- 1.5-AG and glycoalbumin levels under fasting.

Safety - Adverse events reported such as hypoglycemia (severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, nocturnal hypoglycemia), treatment-emergent adverse events (TEAEs), serious TEAEs. Safety was also assessed through vital signs, 12-lead electrocardiogram (ECG), hematology, serum chemistry, lipid parameters, amylase, lipase and urinalysis.

Pharmacodynamics - Change in gastric emptying rate from baseline to Day 29.

Pharmacodynamics sampling times and bioanalytical methods - Breath gas under standardized tolerance test was collected just before standardized breakfast as well as at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, and 4 hours after standardized breakfast.

Statistical methods:

Efficacy analysis - The primary efficacy population was the modified intention-to-treat (mITT) population, which included patients randomized and exposed to at least one dose of the investigational medicinal product (IMP), and had both a baseline measurement and at least one post-baseline measurement of any efficacy variables. All efficacy variables including the primary endpoint (change in PPG [$AUC_{0:00-4:00h}$] after a standardized breakfast from baseline to Day 29) were analyzed using an analysis of covariance (ANCOVA) model with treatment groups, randomization strata of screening SU use (Yes, No) as fixed effects and the baseline value of the corresponding variable as a covariate. The least squares (LS) mean changes in each variable from baseline to Day 29 for each treatment group were provided in the framework of this model, as well as the difference between treatment groups and the 95% confidence interval (CI) for the LS mean. The statistical test for the primary efficacy variable was set at a (two-sided) 5% significance level. Descriptive statistics and graphs for each variable were also provided.

Safety analysis - All safety analyses were performed on the intention-to-treat (ITT) population, which was defined as all patients randomized and exposed to at least one dose of the IMP. Treatment-emergent adverse events were defined as adverse events that developed or worsened or became serious during the period from the first administration of the IMP up to 3 days after the last administration of the IMP. The summary of safety results was descriptive and presented by each treatment group.

Pharmacodynamics analysis - The analysis population for the PD variable (ie, gastric emptying rate) was the PD population, which was defined as all patients who signed the informed consent for the gastric emptying rate test, who were randomized and exposed at least one dose of the IMP and who performed the gastric emptying rate test at both Visit 2 and Visit 5. Two gastric emptying rate parameters (t_{max} and $t_{1/2b}$) were analyzed using rank ANCOVA model with treatment groups, randomization strata of screening SU use (Yes, No) as fixed effects and the ranked baseline value as a covariate. These parameter values were estimated by the appropriate non-linear model, and converged values were used in this analysis.

Summary:

Population characteristics:

A total of 184 patients with type 2 diabetes mellitus were screened and 136 patients were randomized in this study. Of them, 69 patients were randomized in the lixisenatide group and 67 patients were randomized in the sitagliptin group. All treated patients (n=136) received treatment as per randomization. One patient (sitagliptin group) was excluded from the mITT population due to lack of valid efficacy data.

Two patients (2.9%) in the lixisenatide group and 1 patient (1.5%) in the sitagliptin group prematurely discontinued treatment with IMPs. The reason for IMP discontinuation in 2 patients in the lixisenatide group was due to AEs, whereas 1 patient in the sitagliptin group discontinued treatment with IMPs due to the reasons other than AE (withdrawal by patient and other reason).

Sixty-two patients signed informed consent for the gastric emptying rate test and 45 patients were randomized and treated. Among them, 43 patients (20 and 23 patients in the lixisenatide and sitagliptin groups, respectively) performed the gastric emptying rate test at Visit 2 and Visit 5 (PD population). Two patients (1 patient in each group) were excluded from the PD population due to no gastric emptying rate test at Visit 5.

The demographic and baseline characteristics were not substantially different across the both groups. In the ITT population, median of age was 59.0 years in the lixisenatide group and 61.0 years in the sitagliptin group, and the median of body weight was 62.90 kg in the lixisenatide group and 67.30 kg in the sitagliptin group.

Efficacy results:

Treatment with lixisenatide resulted in a statistically significant decrease in PPG ($AUC_{0:00-4:00h}$) from baseline to Day 29 compared to treatment with sitagliptin. The LS mean changes in PPG ($AUC_{0:00-4:00h}$) from baseline to Day 29 were -347.3 h·mg/dL (95%CI: -383.22 to -311.42 h·mg/dL) for the lixisenatide group and -113.3 h·mg/dL (95%CI: -149.48 to -77.15 h·mg/dL) for the sitagliptin group (LS mean difference: -234.0 h·mg/dL, 95%CI: -285.02 to -183.00 h·mg/dL, p-value: < 0.0001).

Treatment with lixisenatide also resulted in a reduction in the maximum PPG excursion (LS mean difference: -75.8 mg/dL, 95%CI : -93.80 to -57.81 mg/dL), C-peptide ($AUC_{0:00-4:00h}$) (LS mean difference: -5.8 h·ng/mL, 95%CI: -7.10 to -4.44 h·ng/mL) and glycoalbumin (LS mean difference: -0.73%, 95%CI: -1.318% to -0.139%) compared to treatment with sitagliptin. No difference in the change in glucagon ($AUC_{0:00-4:00h}$) and fasting 1.5-AG was observed between the treatment groups.

Safety results:

Treatment-emergent adverse events were reported more frequently with lixisenatide compared to sitagliptin (42 patients [60.9%] and 11 patients [16.4%] in the lixisenatide and sitagliptin groups, respectively).

All TEAEs were mild or moderate in intensity. Common TEAEs in the lixisenatide group were those in gastrointestinal disorders systemic organ class (SOC) which were more frequent than in the sitagliptin group (32 patients [46.4%] and 1 patient [1.5%] in the lixisenatide and sitagliptin groups, respectively). Other TEAEs observed more frequently with lixisenatide than sitagliptin were those in metabolism and nutrition disorders SOC (14 patients [20.3%] and 1 patient [1.5%] in the lixisenatide and sitagliptin groups, respectively). In preferred term, nausea (22 patients [31.9%] and 0 patient [0%] in the lixisenatide and sitagliptin groups, respectively) and hypoglycaemia (11 patients [15.9%] and 1 patient [1.5%] in the lixisenatide and sitagliptin groups, respectively) were more frequently reported as TEAEs in the lixisenatide group than in the sitagliptin group.

No death or serious TEAE occurred during the study.

Treatment-emergent adverse events leading to permanent treatment discontinuation were reported in 2 patients (2.9%) in the lixisenatide group and 0 patients (0%) in the sitagliptin group. Of these two patients in the lixisenatide group, 1 patient experienced dysgeusia, nausea and hypoaesthesia oral, and the other patient experienced vomiting as TEAEs leading to permanent treatment discontinuation.

Any hypoglycemia as per protocol definition was reported in 11 patients (15.9%) in the lixisenatide group and 1 patient (1.5%) in the sitagliptin group. A total of 7 patients (10.1%) in the lixisenatide group and 1 patient (1.5%) in the sitagliptin group experienced documented symptomatic hypoglycemia. In patients with SU, 4 patients (12.1%) in the lixisenatide group experienced documented symptomatic hypoglycemia. In patients without SU, 3 patients (8.3%) in the lixisenatide group and 1 patient (2.9%) in the sitagliptin group experienced documented symptomatic hypoglycemia. Only patients without SU in the lixisenatide group occurred asymptomatic hypoglycemia (4 patients [11.1%]). No severe hypoglycemia occurred in either treatment group.

One adverse event of special interest (AESI) (electrocardiogram QT prolonged) was reported in the lixisenatide group. The grade of this event was mild.

As for vital sign, ECG and laboratory values, no clinically relevant abnormal change was reported except for the above mentioned 1 AESI.

Pharmacodynamic results:

Six patients in the lixisenatide group and 1 patient in sitagliptin group performed the gastric emptying rate test at Visit 5, but the gastric emptying rate parameter values were not converged.

Mean changes in t_{max} of gastric emptying rate from baseline to Day 29 were 2.654 (hr) for the lixisenatide group and 0.002 (hr) for the sitagliptin group. Mean changes in $t_{1/2b}$ of gastric emptying rate from baseline to Day 29 were 8.146 (hr) for the lixisenatide group and 0.171 (hr) for the sitagliptin group. Differences between the treatment groups for the both variables were statistically significant.

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