*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<br>**Drug substance(s):** Lixisenatide (AVE0010) | **Study Identifiers:** NCT01596504, UTN 1111-1124-1364<br>EudraCT 2012-000027-40<br>**Study code:** PDY12625 |

**Title of the study:** An open-label, randomized, three-parallel-group study on pharmacodynamic effects of 8-week QD treatment with lixisenatide compared to liraglutide in patients with type 2 diabetes not adequately controlled with insulin glargine with or without metformin (PDY12625)

**Study center(s):** Multicenter (8 centers in Germany)

**Study period:**

Date first patient enrolled: 22/May/2012

Date last patient completed: 25/July/2013

**Phase of development:** Phase 2

**Objectives:**

**Primary objective:** To investigate the effects of repeated subcutaneous doses of lixisenatide 20 µg once daily (QD) as compared to liraglutide 1.2 mg QD or 1.8 mg QD in reducing postprandial plasma glucose assessed as area under the plasma glucose concentration-time curve after a standardized breakfast at the end of an 8-week treatment period in patients with type 2 diabetes mellitus (T2DM) not adequately controlled with insulin glargine (± metformin).

**Secondary objectives:**

- To assess the effects of lixisenatide 20 µg QD as compared to liraglutide 1.2 mg QD or 1.8 mg QD after an 8-week treatment period in patients with T2DM not adequately controlled with insulin glargine (± metformin) on:
  - Plasma glucose concentration over 24 hours
  - Fasting plasma glucose (FPG)
  - 7-point self-monitored plasma glucose (SMPG)
  - Postprandial C-peptide and glucagon after a standardized breakfast
  - Glycosylated hemoglobin ($HbA_{1c}$)
  - Average daily dose of insulin glargine
  - Gastric emptying after a standardized labeled test meal
  - 24-hour heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP)
  - Body weight and waist circumference
  - Visual analog scale (VAS) for assessment of appetite perceptions after standardized dinner and breakfast
- To assess lixisenatide and liraglutide safety and tolerability as add-on treatment to insulin glargine (± metformin)

**Methodology:** Multicenter, randomized, open-label, comparator-controlled, repeated-dose study with 3-arm parallel group design.

The patients were stratified by Day-7 values of $HbA_{1c}$ (<8%, ≥8%), the use of metformin (yes/no), and the centers.

| | |
|---|---|
| **Number of** patients**:** | Planned: Approximately 140 patients |
| | Randomized: 142 |
| | Treated: 142 |
| **Evaluated:** | |
| | Pharmacodynamics: 136 |
| | Safety: 142 |

**Diagnosis and criteria for inclusion:** Male and female patients with T2DM diagnosed at least 1 year before the screening visit, insufficiently controlled with stable doses of neutral protamine hagedorn or insulin glargine alone or in combination with a stable dose of metformin and with $HbA_{1c}$ ≥6.5% and ≤9.5% at screening.

**Study treatments**

**Investigational medicinal product(s):** Lixisenatide

**Formulation:** Aqueous solution (100 µg/mL) for injection in a 3-mL glass cartridge

**Route(s) of administration:** Subcutaneous injection with the pen-type injector (Opticlik®)

**Dose regimen:** Patients in Group A received an initial QD dose of lixisenatide 10 µg for 2 weeks, followed by a maintenance QD dose of lixisenatide 20 µg up to Day 57 (end of the treatment period). Lixisenatide was administered in the morning in fasted conditions (approximately 30 minutes prior to breakfast).

**Investigational medicinal product(s):** Liraglutide

**Formulation:** Solution (6 mg/mL)

**Route(s) of administration:** Subcutaneous injection with prefilled pen Victoza®

**Dose regimen:** Patients in Group B received an initial QD dose of liraglutide 0.6 mg for 1 week followed by a maintenance QD dose of liraglutide 1.2 mg up to Day 57. Patients in Group C received an initial QD dose of liraglutide 0.6 mg for 1 week, then a QD dose of 1.2 mg for 1 week followed by the maintenance QD dose of 1.8 mg up to Day 57. In both groups, liraglutide was administered in the morning in fasted conditions (approximately 30 minutes prior to breakfast).

**Noninvestigational medicinal product(s):** Insulin glargine (Lantus®)

**Formulation:** Solution (100 international unit [IU]/mL)

**Route(s) of administration:** Subcutaneous injection with prefilled Lantus SoloSTAR® pen

**Dose regimen:** Patients selected in this study were treated prior to screening with insulin glargine or neutral protamine hagedorn (background therapy) for at least 3 months and at a stable dose of at least 10 units (U) per day (for at least 2 months prior to screening) ± metformin. If patients were receiving their insulin with metformin combined with a dipeptidyl peptidase-4 inhibitor or a sulfonylurea, patients had to discontinue the dipeptidyl peptidase-4 inhibitor or sulfonylurea from their entry into the run-in phase and were maintained only on insulin glargine ± metformin alone. The metformin dose remained unchanged throughout the study period.

During the run-in phase, insulin glargine was titrated individually once per week for a maximum of 11 weeks according to an algorithm based on the results of fasting SMPG levels. Insulin glargine was always administered QD at approximately the same clock time as was usually done by the patient.

After this forced titration phase, insulin glargine doses were adjusted throughout the remaining part of the study to maintain the patient's FPG in a target range between 4.4 and 5.6 mmol/L (80 and 100 mg/dL).

If $HbA_{1c}$ on Day -7 was ≥6.5% and ≤7.5%, the insulin glargine dose was to be reduced by 20% the day before the randomization (Day -1) in order to avoid hypoglycemia when starting the combination therapy with lixisenatide or liraglutide.

**Noninvestigational medicinal product(s):** 13-carbon ($^{13}C$)-octanoic acid

**Formulation:** Liquid

**Route of administration:** Oral

**Dose regimen:** Standardized breakfast (for gastric emptying assessment) containing 91 mg of ($^{13}C$)-octanoic acid incorporated into an egg was administered before treatment (Day -4) and at the end-of-study treatment (Day 55).

**Duration of treatment:** 8 weeks and 1 day (57 days)

**Duration of observation:** Total study duration of approximately 23 weeks including: screening (up to 2 weeks), a run-in period (a maximum of 12 weeks), treatment period (8 weeks and 1 day [57 days]), and a follow-up (5 to 9 days after the last treatment day).

**Criteria for evaluation:**

Pharmacodynamics:

Primary: Change in postprandial plasma glucose (PPG) from baseline to Day 56 based on the area under the plasma glucose concentration time profile from time of standardized breakfast start (30 minutes after investigational medicinal product [IMP] injection = T0H30) until 4 hours later (T4H30), subtracting the pre meal plasma glucose value (corrected PPG area under curve [$AUC_{0:30\text{-}4:30h}$]).

Secondary:

- Change in $AUC_{0:30\text{-}5:30h}$ from baseline to Day 56 for plasma glucose, C-peptide, and glucagon - $AUC_{0:30\text{-}5:30h}$: area under the concentration time profile from the time of standardized breakfast start (30 minutes after IMP injection=T0H30) until 5 hours later (T5H30) where the pre meal values (T0H30) were subtracted from concentrations. The area under the plasma glucose-concentration-time curve was calculated using the trapezoidal rule.
- Change from baseline (Day -3) to Day 56 for the maximum PPG excursion (ie, the maximum changes in PPG relative to the premeal plasma glucose concentration determined from time of breakfast start until 5 hours later [T5H30])
- Number of patients with 2-hour PPG level <7.77 mmol/L (140 mg/dL) on Day 56
- The 24-hour profile of plasma glucose (17 time points), C-peptide, and glucagon (11 time points each) concentrations on Day -3/Day -2 and Day 56/Day 57 in raw data
- Change in FPG concentration from baseline (Day -3, T0H30 prior to breakfast) to Day 56
- 7-point SMPG profiles at the first start day of the run-in period, Day -3, Day 28, and Day 56
- Change in time-matched baseline (Day -3) to Day 56 for 7-point SMPG
- Change from baseline (Day -3) to Day 56 for the mean 7-point SMPG
- HbA1c change from baseline (Day 1) to Day 56
- Percentage of patients with $HbA_{1c}$ <7% on Day 56
- Percentage of patients with $HbA_{1c}$ ≤6.5% on Day 56
- Change in average daily insulin glargine dose from Day -7 to Day 56
- Gastric emptying from 13C-octanoic acid breath test: change from baseline (Day -4) to Day 55

  - Lag phase ($t_{lag}$): time at which the percentage (%) of dose reached its peak

  - Emptying half-life ($t_{1/2}$): time at which $^{13}C$ retention has declined to 50%

  - Gastric emptying coefficient: derived from a mathematical formula that describes the gastric-emptying rate and gives an overall index of gastric emptying.

- Change from baseline (Day -2) to Day 57 for mean 24-hour and day/night time HR, SBP, and DBP
- Change from baseline (Day -1) to Day 57 for body weight and waist circumference
- Each individual for VAS scores ("How hungry do you feel?", "How satisfied do you feel?", "How full do you feel?", "How much do you think you can eat?") was analyzed separately after standardized breakfast on Day -3 and Day 56. Each score was computed in raw data and changes from baseline determined using the 2 following ways:

  - By averaging time point across Day -3 (for the baseline value) and Day 56

  - Using each time point values for Day -3 and Day 56 and the change from baseline by time-matching (the value corresponding to the same time of Day -3).

The same analyses were conducted using VAS values assessed after standardized dinner on Day -4 and Day 55.

**Safety:** Patients were monitored for safety via adverse events (AEs; including, in particular, symptomatic and severe symptomatic hypoglycemia, local tolerability at injection site, allergic or allergic-like reactions, suspected pancreatitis, and major cardiovascular events), physical examination, body temperature, vital signs, clinical laboratory evaluations, and standard 12-lead electrocardiograms (ECGs).

**Pharmacodynamics sampling times and bioanalytical methods:** Blood samples for pharmacodynamic (PD) analysis were collected on: Day -3 (baseline) and Day 56 for plasma glucose, glucagon, and C-peptide assessments. Blood samples were taken 30 minutes before a standardized solid breakfast and prior to dosing (T0; Day 56 only), then immediately prior to the standardized breakfast (T0.5 hours), and thereafter at T0.67, T0.83, T1, T1.50, T2, T2.5, T3.5, and T4.5 (ie, 10, 20, 30, 60, 90, 120, 180, and 240 minutes post breakfast) for glucose-$AUC_{0:30\text{-}4:30h}$, up to T5.5 (prior to lunch for $AUC_{0:30\text{-}5:30h}$ for glucose, glucagon, and C-peptide measurement), and continued at T7.5, T8.5, T10.5, T12.5 (prior to dinner), T14.5, and T24 (prior to breakfast) for assessment of the 17-time point plasma glucose concentrations (24-hour plasma glucose profile).

Blood samples were collected at screening, Day -7, Day 1 (baseline), Day 28, and Day 56 for $Hb_{A1c}$ assessment. The analyses were performed on samples stored at ambient temperature (at screening and Day -7) and in frozen conditions (on Day 1, Day 28, and Day 56).

Seven-point SMPG (before breakfast, 2 hours post breakfast, before lunch, 2 hours post lunch, before dinner, 2 hours post dinner, and at bedtime) were performed at the first start day of the run-in period, on Day -3, Day 28, and Day 56.

On Day -4 (baseline) and Day 55, breath samples ($^{13}C$-labeled carbon dioxide) were collected 30 minutes before the test meal (and prior to dosing on Day 55), every 15 minutes after breakfast during 2 hours, then every 30 minutes during the following 3 hours (in total 15 samples) for gastric emptying evaluation.

The quantitative analysis of plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay for glucose from Roche Diagnostics, Mannheim (Germany). The range of the method was 3 to 1000 mg/dL, with 1 mg/dL as limit of detection, 3 mg/dL as lower limit of quantification, and 1000 mg/dL as upper limit of quantification.

The method for quantitative analysis of human C-peptide was assessed using the Electro Chemiluminescence Immunoassay for C-peptide from Roche Diagnostics, Mannheim (Germany). The range of the method was 0.2 to 25 ng/mL, with a lower limit of quantification of 0.2 ng/mL and a limit of detection of 0.07 ng/mL.

The method for quantitative analysis of glucagon was assessed using the radioimmunoassay for glucagon from Euro Diagnostica, Malmö (Sweden). The range of the method was 4.7 to 150 pmol/L.

The quantitative method of $HbA_{1c}$ was assessed according to applicable international standards from the Food and Drug Administration and European Medicines Agency using the high-performance liquid chromatography method from Tosoh Corporation, Tokyo (Japan). The maximal intra assay imprecision was observed with a coefficient of variance of 0.97%. The maximal inter assay imprecision was observed with a coefficient of variance of 0.39%.

Self-monitored plasma glucose was done using Freestyle Precision glucometer (Abbott, Germany).

Gastric emptying breath samples were analyzed for $^{13}C$-labeled carbon dioxide by isotope-selective non-dispersive infrared spectrometry (IRIS; Wagner, Analysen Technik, Bremen, Germany).

The 24-hour ambulatory blood pressure and HR were measured using an ambulatory blood pressure monitor (model 90207; SpaceLabs, Inc.; Redmond, WA).

**Statistical methods:**
**Pharmacodynamics:**

The PD population was the modified intent-to-treat population, which included all randomized patients, who received at least 1 dose of IMP and had both a baseline assessment and at least 1 post baseline assessment of any primary or secondary PD variables, irrespective of compliance with the study protocol and procedures.

The statistical analysis for the primary PD endpoint (changes from baseline to Day 56 [Week 8] in corrected PPG $AUC_{0:30-4:30h}$) compared lixisenatide 20 µg to liraglutide 1.2 mg or lixisenatide 20 µg to liraglutide 1.8 mg at the 1-sided overall alpha level of 0.05, using the procedure of Hochberg to ensure type I error control. All continuous PD parameters including the primary endpoint were analyzed using a linear model with treatment and stratification factors ($HbA_{1c}$, the use of metformin, and center) as fixed effects and using the baseline value of the corresponding parameter as a covariate. Differences between treatment groups and confidence intervals (CIs) were estimated within the model framework.

**Safety:**

The safety analysis was conducted on the safety population, defined as all randomized patients who received at least 1 dose of IMP (regardless of the amount of treatment administered). The safety analysis was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables and plots if appropriate) by treatment.

The on-treatment period was defined as the time from the first IMP injection up to 3 days after the last IMP injection.

Adverse events were classified in system organ classes and preferred terms (Medical Dictionary from Regulatory Activities, version 16.0), and the number of patients with treatment-emergent adverse events (TEAEs) was summarized by treatment.

Potentially clinically significant abnormalities (version dated 14 September 2009) for clinical laboratory, vital signs, and ECG data were summarized in frequency tables by treatment. Potentially clinically significant abnormalities that occurred after the first dosing were listed by parameter, treatment, and patient.

**Summary:**

**Population characteristics:** A total of 142 T2DM patients were randomized to 1 of the 3 treatment groups (48 in the lixisenatide 20 µg group, 47 in the liraglutide 1.2 mg group, and 47 in the liraglutide 1.8 mg group). All patients randomized were exposed to IMP (safety population) and 136 were included in the modified intent-to-treat population. Demographics and baseline characteristics were generally similar across the treatment groups. The study population was primarily Caucasian (99.3%) with a median age of 63 years. Most patients were overweight/obese with mean weights comparable among the treatment groups, with an overall population mean weight of 91.69 kg and an overall median body mass index of 29.94 $kg/m^2$.

Insulin glargine was optimally titrated during the run-in phase, with median insulin glargine daily doses of 39.0, 38.0, and 43.0 U on Day -7 in the lixisenatide and the liraglutide 1.2 and 1.8 mg groups, respectively, and mean FPG values of 5.33, 5.20 and 5.34 mmol/L (96.09, 93.75, and 96.27 mg/dL) on Day -3 in the lixisenatide group and the liraglutide 1.2 and 1.8 mg groups, respectively.

Overall, 87.3% of patients in the study population had $HbA_{1c}$ values <8% at Day -7 with a mean of 7.22%, 7.19%, and 7.33% in the lixisenatide and liraglutide 1.2 and 1.8 mg groups, respectively.

Almost all patients were compliant to treatment. The average IMP treatment exposure (in combination with insulin glargine ± metformin) was 56.1, 55.6, and 56.3 days in the lixisenatide and liraglutide 1.2 and 1.8 mg groups, respectively.

**Pharmacodynamic results**: Pharmacodynamic data were assessed at baseline and at the end of treatment period (Day 56 [Week 8]).

Lixisenatide provided a significantly greater reduction in PPG after a standardized solid breakfast compared to liraglutide 1.2 mg and liraglutide 1.8 mg. For the primary endpoint (corrected PPG $AUC_{0:30-4:30h}$), the least squares (LS) mean difference between lixisenatide and liraglutide 1.2 mg was 6.01 h.mmol/L; 95% one-sided CI: 7.77 h.mmol/L (-108.33 h.mg/dL; 95% one-ided CI: -139.96 h.mg/dL) (p <0.0001) and the difference between lixisenatide and liraglutide 1.8 mg was 4.61 h.mmol/L; 95% one-sided CI: 6.34 h.mmol/L (-83.03 h.mg/dL; 95% one-sided CI: -114.22 h.mg/dL) (p<0.0001).

A greater percentage of patients treated with lixisenatide (35 patients [76.1%]) achieved 2-hour PPG concentrations <7.77 mmol/L (140 mg/dL) after a standardized solid breakfast on Day 56 compared to patients treated with liraglutide 1.2 mg (13 patients [29.5%]) and with liraglutide 1.8 mg (11 patients [23.9%]).

Lixisenatide significantly reduced the maximum PPG excursion during the postprandial period up to 5 hours after breakfast, compared to liraglutide: the LS mean difference between lixisenatide and liraglutide 1.2 mg was -1.47 mmol/L; 95% CI: 2.22 to -0.72 mmol/L (-26.49 mg/dL; 95% CI: 40.06 to -12.92 mg/dL) (p=0.0002) and between lixisenatide and liraglutide 1.8 mg was 0.76 mmol/L; 95% CI: 1.50 to -0.01 mmol/L (-13.60 mg/dL; 95% CI: 26.96 to -0.25 mg/dL) (p=0.0460).

An overall reduction in plasma glucose was observed on the 24-hour glucose profiles (17 points) in the 3 treatment groups. Greatest reductions with lixisenatide were seen postbreakfast (up to 4 hours and 30 minutes after injection of IMP). Treatment with liraglutide (1.2 and 1.8 mg) resulted in consistent glucose reductions throughout the day.

Plasma 7-point SMPG profiles showed a similar pattern to the 24-hour plasma glucose profile.

Lixisenatide substantially slowed gastric emptying as shown by the analyses of breath parameters $t_{lag}$ and $t_{1/2}$. Lixisenatide increased mean $t_{lag}$ and $t_{1/2}$ by 175.56 and 453.56 minutes (LS mean changes from baseline), respectively. These increases were significantly greater than those seen with liraglutide: LS mean increases of $t_{1/2}$ and $t_{lag}$ were 70.10 and 175.31 minutes and 48.85 and 130.49 minutes in the liraglutide 1.2 and 1.8 mg groups, respectively. Treatment differences were statistically significant (p <0.0001).

Corrected postprandial C-peptide $AUC_{0:30-5:30h}$ was significantly reduced with lixisenatide but was increased with both liraglutide doses: the LS mean difference between lixisenatide and liraglutide 1.2 mg was 2.39 h.nmol/L; 95% CI: -3.10 to 1.69 h.nmol/L (-7.19 h.ng/mL; 95% CI: -9.30 to -5.08 h.ng/mL) and the difference between lixisenatide and liraglutide 1.8 mg was -2.04 h.nmol/L; 95% CI: 2.73 to 1.35 h.nmol/L ( 6.13 h.ng/mL; 95% CI: -8.21 to -4.06 h.ng/mL); both differences were statistically significant (p <0.0001).

The LS mean difference for corrected postprandial glucagon $AUC_{0:30-5:30h}$ between lixisenatide and liraglutide 1.2 mg was 8.15 .ng/L; 95% CI: -64.97 to 8.68 h.ng/L ( 28.15 h.pg/mL; 95% CI: -64.97 to 8.68 h.pg/mL) and the difference between lixisenatide and liraglutide 1.8 mg was -22.16 h.ng/L; 95% CI: -58.26 to 13.93 h.ng/L ( 22.16 h.pg/mL; 95% CI: 58.26 to 13.93 h.pg/mL). These differences were not statistically significant.

Fasting plasma glucose remained stable during the treatment period in all treatment groups with LS mean changes from baseline of 0.10, 0.12, and 0.13 mmol/L (1.82, 2.25, and 2.31 mg/dL) for lixisenatide, liraglutide 1.2 mg, and liraglutide 1.8 mg, respectively.

Mean $HbA_{1c}$ decreased in all treatment groups: LS mean changes from baseline to Day 56 in the lixisenatide group and liraglutide 1.2 and 1.8 mg groups were -0.58% (95% CI: -0.69% to -0.47%), 0.66% (95% CI: -0.77% to 0.55%), and 0.74% (95% CI: 0.85% to -0.62%), respectively. The LS mean difference between lixisenatide and liraglutide 1.2 mg was 0.08% (95% CI: 0.03% to 0.20%) (not statistically significant) and the difference between lixisenatide and liraglutide 1.8 mg was 0.16% (95% CI: 0.04% to 0.27%) (p=0.0070).

Mean body weight and waist circumference decreased in all groups: LS mean changes from baseline for body weight were 1.61 kg in the lixisenatide group versus -1.78 and 2.42 kg in the liraglutide 1.2 and 1.8 mg groups, respectively. Treatment differences were not statistically significant.

The average daily dose of insulin glargine was decreased similarly in all treatment groups on Day 56 when compared to Day -7 (baseline): mean change from 42.5 to 37.8 U, from 40.7 to 36.1 U, and from 44.9 to 40.9 U for lixisenatide, liraglutide 1.2 mg, and liraglutide 1.8 mg, respectively.

Mean 24-hour HR assessed by ambulatory monitoring showed a lower increase in the lixisenatide group compared to the liraglutide groups: LS mean changes from baseline were 3.34 bpm for lixisenatide versus 9.33 and 9.17 bpm for liraglutide 1.2 and 1.8 mg, respectively. The LS mean differences between the lixisenatide group and the liraglutide groups were statistically significant (p <0.0001): 5.98 bpm (95% CI: 3.73 to 8.24 bpm) for lixisenatide versus liraglutide 1.2 mg and 5.83 bpm (95% CI: 3.62 to 8.04 bpm) for lixisenatide versus liraglutide 1.8 mg. Changes in mean 24-hour SBP and DBP were minimal in all treatment groups.

Change from time-matched baseline for appetite perception (VAS) was similar in the 3 treatment groups. Patients tended to feel more satisfied, to feel fuller, and to think they could eat less after standardized breakfast at Day 56 (Week 8) compared to baseline.

**Safety results:** The overall incidence of TEAEs was similar in all treatment groups: 33 (68.8%) in the lixisenatide group and 31 (66.0%) in both liraglutide 1.2 and 1.8 mg groups. Gastrointestinal AEs were less frequent in the lixisenatide group (35.4%) than in the liraglutide 1.2 mg (44.7%) and the liraglutide 1.8 mg (46.8%) groups. The difference was mainly due to a higher incidence of diarrhea, constipation, and abdominal distension in the liraglutide 1.2 and 1.8 mg groups, and upper abdominal pain in the liraglutide 1.8 mg group. The most frequently reported TEAEs were decreased appetite (9 [18.8%] patients in the lixisenatide group versus 9 [19.1%] patients in the liraglutide 1.2 mg group and 13 [27.7%] patients in the liraglutide 1.8 mg group) and nausea (9 [18.8%] patients in the lixisenatide group versus 8 [17.0%] patients in the liraglutide 1.2 mg group and 11 [23.4%] in the liraglutide 1.8 mg group).

Symptomatic hypoglycemia events (including documented, probable, and severe symptomatic hypoglycemia) were collected in a specific AE form and were reported in 14 (29.2%), 9 (19.1%), and 10 (21.3%) patients of the lixisenatide and the liraglutide 1.2 and 1.8 mg groups, respectively. The number of symptomatic hypoglycemia events per patient-year was 4.36, 1.87, and 2.90 in the lixisenatide and the liraglutide 1.2 and 1.8 mg groups, respectively. One severe hypoglycemia event occurred in a lixisenatide-treated patient.

No death was reported in this study.

Two patients experienced treatment-emergent serious AEs. One patient treated with lixisenatide experienced coronary artery disease on Day 33 and the percutaneous coronary intervention was positively adjudicated by the Cardiovascular Events Adjudication Committee. One patient treated with liraglutide 1.2 mg had a myocardial infarction on Day 22 and the event was positively adjudicated by the Cardiovascular Events Adjudication Committee as myocardial infarction and urgent percutaneous coronary intervention (coronary revascularization procedure).

No patients had TEAE adjudicated as allergic reaction by the Allergic Reaction Assessment Committee.

Four patients had TEAEs leading to treatment discontinuation: 1 patient in the lixisenatide group due to nausea, vomiting, and fatigue; 2 patients in the liraglutide 1.2 mg group (1 for myocardial infarction, and 1 for abdominal pain); and 1 patient in the liraglutide 1.8 mg group for dyspepsia.

Mean changes from baseline to Day 56 (Week 8) in lipase levels were 6.83 IU/L in the lixisenatide group compared to 21.07 and 21.61 IU/L in the liraglutide 1.2 and 1.8 mg groups, respectively. The LS mean differences between lixisenatide and liraglutide 1.2 and 1.8 mg on changes from baseline to Day 56 were statistically significant (p=0.0386 and 0.0395, respectively). A case of asymptomatic mild oedematous pancreatitis was diagnosed by magnetic resonance imaging in 1 patient (2.1%) with elevated lipase levels in the liraglutide 1.8 mg group.

Increase from baseline in HR assessed by ECG was less pronounced in the lixisenatide group than in the liraglutide 1.2 and 1.8 mg groups (1.2, 8.1, and 8.8 beat per minute [bpm], respectively). This finding is consistent with the increases in mean 24-hour HR assessed by ambulatory monitoring. Diastolic and systolic blood pressure data and assessment of ECG readings did not reveal any safety signal.

**Issue date:** 11-Jul-2014