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Sponsor: Sanofi **Drug substance(s):** HOE901/AVE0010	**Study Identifiers:** U1111-1148-4351, NCT02058160 & 2013-003132-79 **Study code:** EFC12405
Title of the study: A randomized, 30 week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination to insulin glargine with or without metformin in patients with Type 2 diabetes mellitus (T2DM)	
Study center(s): 187 centers in 18 countries	
Study period: Date first patient enrolled: 27/Jan/2014 Date last patient completed: 09/Jul/2015	
Phase of development: Phase 3	

Objectives:

Primary objective:

To demonstrate the superiority of the insulin glargine/lixisenatide fixed ratio combination (hereafter referred to as FRC) to insulin glargine in glycated hemoglobin (HbA1c) change from baseline to Week 30.

Secondary objectives:

- To assess the effects of the FRC in comparison with insulin glargine over 30 weeks on:
  - Percentage of patients reaching HbA1c targets
  - Glycemic control in relation to a meal as evaluated by 2-hour postprandial plasma glucose (PPG) and glucose excursion during a standardized meal test
  - Body weight
  - 7-point self-monitored plasma glucose (SMPG) profile
  - Percentage of patients reaching HbA1c targets with no body weight gain and/or documented symptomatic hypoglycemia
  - Insulin glargine dose
  - Fasting plasma glucose (FPG)
- To assess the safety and tolerability in each treatment group.
- To assess the development of anti-insulin glargine antibodies (AIAs) and anti-lixisenatide antibodies (ADAs) (in the FRC treatment group only for the latter).
- To assess the total and active plasma concentration of lixisenatide before and following injection (in the FRC treatment group only).
- To assess the treatment effects in each treatment group on patient reported outcomes (PROs) measured by the following questionnaires:
  - Treatment Related Impact Measure-Diabetes (TRIM-D)
  - EuroQol-5 Dimensions version 3L (EQ-5D-3L)
  - Impact of Weight on Quality of Life-Lite (IWQoL-Lite)
- To assess patients' overall response to treatment using patient- and physician-rated global treatment effectiveness evaluation scales for each treatment group.

Methodology:

This was an open-label, 1:1 randomized, active-controlled, 2-group, 30 week treatment duration, parallel-group, multinational, and multicenter study. The randomization was stratified by HbA1c values at Visit 5 (Week -1) (<8%, ≥8%) and metformin use at screening (yes, no).

The study comprised 3 periods:

- An up to 8 week screening period, which included an up to 2 week screening phase and a 6 week run-in phase with switch to (if appropriate) and/or dose titration/stabilization of insulin glargine, continuation of metformin (if appropriate), and discontinuation of sulfonylurea (SU), glinides, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, or dipeptidyl-peptidase-4 (DPP-4) inhibitors if previously taken at Visit 2
- A 30 week open-label randomized treatment period
- A 3-day post-treatment safety follow-up period

Number of patients**:**	Planned: 700 (350 per group)
	Randomized: 736 (FRC: 367, insulin glargine: 369)
	Treated: 730 (FRC: 365, insulin glargine: 365)
Evaluated:	
	Efficacy: 731 (FRC: 366, insulin glargine: 365)
	Safety: 730 (FRC: 365, insulin glargine: 365)
	Pharmacokinetics: 356 (FRC only)

Diagnosis and criteria for inclusion: Inclusion criteria: Patients with T2DM diagnosed for at least 1 year and inadequately controlled on their current antidiabetic treatment. Patients had to be treated with basal insulin for at least 6 months at a stable daily dose of 15 to 40 U/day for at least 2 months, alone or combined with 1 or 2 oral antidiabetic drugs (OAD) (metformin, SU, glinide, DPP-4 inhibitor, or SGLT 2 inhibitor) at a stable dose for at least 3 months.

Key exclusion criteria for randomization (at the end of the screening period): HbA1c <7% or >10% at Visit 5 (Week 1); mean fasting SMPG >140 mg/dL (7.8 mmol/L) for the 7 days before the randomization visit (Visit 6); average insulin glargine daily dose <20 or >50 U calculated for the last 3 days before Visit 6.

Study treatments

Investigational medicinal product(s): FRC and insulin glargine (Lantus)

Formulation:

Insulin glargine/lixisenatide fixed ratio combination

The FRC was supplied as a sterile aqueous solution in a pre-filled disposable SoloStar® pen injector. Two pens (A and B) with different insulin glargine/lixisenatide fixed ratios were available to allow insulin glargine titration over a range of 10 to 60 U/day while limiting the lixisenatide dose to a maximum of 20 µg/day:

- Pen A contained 100 U/mL insulin and 50 µg/mL lixisenatide in a ratio of 2 U:1 µg; doses could be set from 10 U to 40 U in steps of 1 U, allowing administration of daily doses between 10 U/5 µg and 40 U/20 µg.
- Pen B contained 100 U/mL insulin glargine and 33 µg/mL lixisenatide in a ratio of 3 U/1 µg; doses could be set from 30 U to 60 U in steps of 1 U, allowing administration of daily doses between 30 U/10 µg and 60 U/20 µg.

The maximum daily dose of FRC was 60 U insulin glargine/20 µg lixisenatide, to be delivered by Pen B.

Insulin glargine

Insulin glargine was supplied as a sterile aqueous solution in a pre-filled disposable Lantus SoloStar pen-injector (100 U/mL). Doses could be set from 1 U to 80 U in steps of 1 U. The maximum daily dose of insulin glargine was limited to 60 U.

Route(s) of administration: Self-administered subcutaneous injection

Dose regimen:

Run-in phase:

From the start of the run-in phase (Visit 2), the only basal insulin allowed was insulin glargine. Patients receiving any basal insulin other than insulin glargine before screening were switched to once daily insulin glargine at Visit 2. Insulin glargine was administered at any time of the day and at around the same time every day. The injection time was selected at Visit 2 at the discretion of the patient and the Investigator and was to remain the roughly the same throughout the study (during the run-in phase for all patients and during the randomized treatment period for patients randomized to insulin glargine).

Open-label randomized treatment period:

Patients randomized to the FRC group injected the FRC once daily in the morning, in the hour (0 to 60 minutes) before breakfast. The recommended starting dose of lixisenatide is 10 µg once daily, to be kept stable for 2 weeks. Therefore, patients switching from insulin glargine to the FRC began treatment at a recommended daily lixisenatide dose of 10 µg using either Pen A (20 U insulin glargine) or Pen B (30 U), depending on the insulin glargine dose received by the patient the day before randomization: if this dose was <30 U, the starting dose of FRC was 20 U/10 µg given with Pen A, and if this dose was ≥30 U, the starting dose of FRC was 30 U/10 µg given with Pen B.

After the initiation period, during titration, in the FRC group, the choice of Pen A or Pen B was based on the required FRC daily dose: Pen A was to be used for daily doses below 40 U and Pen B for doses between 41 and 60 U. For a given dose between 30 U and 40 U it was possible to use either Pen A or Pen B. For this dose range the pen which provided a higher dose of lixisenatide, ie, Pen A was to be chosen as long as it was well tolerated. Otherwise (eg, in case of persistent nausea and/or vomiting), Pen B could be used.

Patients randomized to insulin glargine were to administer the same daily dose of insulin glargine on the day of randomization as the day before randomization, and thereafter the insulin dose was titrated as necessary during the randomized treatment period.

The same dose adjustment algorithm was recommended for the FRC and insulin glargine.

Noninvestigational medicinal product (NIMP): Background treatment with metformin and rescue therapy

Metformin: Dose regimen was in accordance with locally approved label. If previously taken at a stable dose of at least 1500 mg/day or maximal tolerated dose for at least 3 months prior to screening, metformin treatment (commercial tablets, administered orally) was to be continued at a stable dose throughout the study unless prevented by a specific safety issue related to this treatment

Rescue therapy: Routine fasting SMPG and central laboratory alerts on FPG (and HbA1c after Week 12) were required to ensure that glycemic parameters remained below predefined threshold values. If values were above predefined thresholds, and no explanations were found, or appropriate actions failed, or an insulin dose >60 U was necessary to decrease FPG and/or HbA1c below the threshold values, short/rapid-acting insulin was introduced as rescue therapy along with IMP and metformin (if taken).

Duration of treatment: Up to 30 weeks

Duration of observation: Up to 39 weeks (up to 8-week screening period + 30-week randomized treatment period + 3-day post-treatment safety follow-up)

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: Change in HbA1c (%) from baseline to Week 30

Secondary efficacy endpoints:

- Percentage of patients reaching HbA1c $\leq$6.5% at Week 30
- Percentage of patients reaching HbA1c <7% at Week 30
- Change in 2-hour PPG and blood glucose excursion during a standardized meal test from baseline to Week 30; the same variables were also assessed at the time points 30 minutes and 1-hour
- Change in body weight from baseline to Week 30
- Change in FPG from baseline to Week 30
- Change in 7-point SMPG profiles from baseline to Week 30 (each time point and average daily value)
- Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30
- Percentage of patients reaching HbA1c <7% at Week 30 with no documented symptomatic hypoglycemia (plasma glucose $\leq$70 mg/dL [3.9 mmol/L] during the 30 week randomized treatment period)
- Percentage of patients reaching HbA1c <7% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia (plasma glucose $\leq$70 mg/dL [3.9 mmol/L]) during the 30-week randomized treatment period
- Change in daily dose of insulin glargine dose from baseline to Week 30
- Percentage of patients requiring rescue therapy during the 30-week open-label treatment period

Patient reported outcomes:

TRIM-D scores (total and domain scores), EQ-5D-3L variables (single utility indices and perceived health status on visual analog scale [VAS]), IWQoL-Lite scores (total and domain scores), patient- and physician-rated global treatment effectiveness evaluation scales (responses to each question)

Safety:

- Symptomatic hypoglycemia:
  - Documented: typical symptoms of hypoglycemia with a plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L)
  - Severe: event required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
  - Probable: symptoms of hypoglycemia without plasma glucose determination, but was presumably caused by a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L)
- Treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to death, TEAEs leading to treatment discontinuation, adverse events (AEs) of special interest (ie, increase in alanine aminotransferase [ALT], pregnancy, symptomatic overdose with IMP/NIMP), major cardiovascular events, local intolerability at injection site, suspected allergic reactions, pancreatic events (increased amylase/lipase value >2 x upper limit of normal [ULN] confirmed by a repeat measurement, pancreatitis, pancreatic neoplasm), increased calcitonin value ≥20 pg/mL (5.9 pmol/L) confirmed by a repeat measurement, and pen-related events.
- Safety laboratory data: Hematology, clinical chemistry (including lipase/amylase and calcitonin), and urine analysis
- Vital signs and physical examination
- Electrocardiogram
- Immunogenicity (antibody variables): AIA status, titer, and change from baseline during the course of the study, with determination of cross-reactivity with human insulin for AIA positive patients, ADA status and concentration (depending on the treatment group)

Pharmacokinetics:

Total and active plasma concentrations on lixisenatide (FRC group only).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

For determination of total concentration of lixisenatide (bound and unbound to ADAs) plasma samples were analyzed using a validated enzyme-linked immuno-sorbent assay with a lower limit of quantification of 5.5 pg/mL.

For determination of active concentrations of lixisenatide, plasma samples were analyzed using a validated cell-based assay with a lower limit of quantification of 40 pg/mL.

Three blood samples were taken from patients in the FRC group on Day 1 (Visit 6) at 1 to 4 hours after IMP injection (only if IMP was administered in the morning of Day 1) and at the end of treatment Visit (Visit 21, Week 30) before IMP injection as well as 1 to 4 hours after IMP injection.

Statistical methods:

The sample size calculations were based on the primary efficacy variable, change in HbA1c from baseline to Week 30, with the following assumptions: a common standard deviation (SD) of 1.1%, a 0.4% mean difference between the FRC and insulin glargine in change in HbA1c from baseline to Week 30, and a t-test at a 2-sided 5% significance level with at least 95% power. Based on these assumptions, 350 patients per group were needed for this study.

Efficacy analyses were based on modified intent-to-treat (mITT) population using efficacy assessments collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy. The mITT population consisted of all randomized patients who had both a baseline assessment and at least 1 post-baseline assessment of any primary or secondary efficacy variables.

The primary efficacy endpoint was analyzed using a mixed-effect model with repeated measures (MMRM). The MMRM model included the treatment group, randomization strata, visit, treatment-by-visit interaction, and country as fixed-effect factors, and the baseline HbA1c value-by-visit interaction as covariate. The adjusted mean change in HbA1c from baseline to Week 30 for each treatment group was estimated in the framework of this model, as well as the between group difference and the 95% confidence interval (CI) for the adjusted mean.

The following sensitivity analyses were performed for the primary endpoint: analysis of covariance (ANCOVA) with missing data imputed by last observation carried forward (LOCF), ANCOVA on 30 week completers, MMRM model excluding the measurements after receiving the rescue therapy, and MMRM model including only scheduled HbA1c measurements collected during the on-treatment period (defined as the time from the first injection of open-label IMP up to 14 days for HbA1c). Treatment effects across subgroups (race, ethnicity, age group, gender, baseline body mass index (BMI), baseline HbA1c, metformin at screening, country, number of OADs used at screening) were estimated for the primary endpoint using the same MMRM model as described above.

A similar MMRM method or ANCOVA was applied on continuous secondary efficacy endpoints, and the Cochran-Mantel-Haenszel method stratified by randomization strata was applied for categorical efficacy endpoints.

A step-down testing procedure was applied to control the type I error. If the primary endpoint was statistically significant at the 5% level, a hierarchical testing procedure was performed on selected secondary endpoints in the following order: 2 hour plasma glucose excursion, body weight, average 7-point SMPG, percentage of patients reaching HbA1c <7% with no body weight gain at Week 30, daily dose of insulin glargine, percentage of patients reaching HbA1c <7% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia, and FPG. When an endpoint was not statistically significant at the 5% level, subsequent testing was stopped.

Patient reported outcomes were analyzed using a similar MMRM method and descriptive statistics.

Safety analyses were performed on the safety population, which consisted of all randomized patients who received at least 1 dose of IMP, regardless of the amount of treatment received. All safety analyses were descriptive and no testing was planned.

The PK analyses were performed on the PK population, which consisted of all randomized and treated patients who contributed at least 1 valid plasma analysis of lixisenatide. Plasma lixisenatide concentrations (total and active) in patients from the FRC group were listed and summarized by visit and time window and by ADA status using descriptive statistics. The active fraction (active concentration/total concentration) was also summarized.

Summary:

Population characteristics:

A total of 736 patients were randomized to 1 of the 2 treatment groups (367 in the FRC group and 369 in the insulin glargine group). A total of 731 patients were included in the mITT population and 730 patients were exposed to open-label treatment and were included in the safety population.

Demographics and baseline characteristics were generally similar between the 2 treatment groups. The study population was primarily White/Caucasian (91.7%) with a median age of 60 years and mean diabetes duration of about 12 years. The median BMI at screening was about 31 kg/m2 and approximately 59% of the patients had a BMI value ≥30 kg/m2, indicating that most patients were obese.

Efficacy results:

All changes (decreases/increases) and differences were calculated as least squares (LS) mean changes (decreases/increases) and differences (hereafter referred to as changes [decreases/increases] and differences) unless otherwise specified.

Primary efficacy endpoint:

The primary objective of the study was met as statistical superiority of the FRC over insulin glargine was demonstrated in change in HbA1c from baseline to Week 30.

Patients in both groups had an initial mean HbA1c decrease from 8.53% at screening to 8.08% at baseline (post run-in). From this baseline value, HbA1c further decreased by -1.13% for FRC group and by -0.62% for the insulin glargine group, reaching mean HbA1c levels of 6.94% and 7.48% at Week 30, respectively. The difference between the 2 treatment groups was -0.52% (95% CI: 0.633%, -0.397%). Statistical superiority of the FRC over insulin glargine was demonstrated (p<0.0001).

These results were robust across various sensitivity analyses. Subgroup analyses were consistent, and there were no relevant differences in HbA1c changes by ADA or AIA status.

Secondary efficacy endpoints:

The improvement in HbA1c was reflected in the markedly higher proportion of FRC-treated patients reaching prespecified HbA1c target <7% at Week 30 (54.9% compared with 29.6% the insulin glargine group) (p<0.0001). This was also the case for the percentage of patients reaching HbA1c ≤6.5% (33.9% in the FRC group versus 14.2% in the insulin glargine group) (p<0.0001).

Treatment with the FRC significantly improved postprandial glycemic control after a standardized liquid breakfast in comparison to insulin glargine as shown by the results of change from baseline to Week 30 in 2-hour glucose excursion (3.90 mmol/L [70.24 mg/dL] with FRC and -0.47 mmol/L [-8.42 mg/dL] with insulin glargine). The difference between the treatment groups was -3.43 mmol/L (-61.82 mg/dL) (p<0.0001). There was also a substantially greater reduction from baseline in 2-hour PPG for the FRC group (4.72 mmol/L [-85.11 mg/dL]) compared to the insulin glargine group (-1.39 mmol/L [25.09 mg/dL]): the mean treatment difference was -3.33 mmol/L (95% CI: -3.889, -2.774 mmol/L; excluding 0) (-60.02 mg/dL; 95% CI: 70.066 mg/dL, 49.969 mg/dL; excluding 0).

Body weight decreased from baseline to Week 30 in the FRC group (-0.67 kg) and increased in the insulin glargine group (+0.70 kg), leading to a statistically significant difference of -1.37 kg (p<0.0001).

Patients in the FRC group reported a statistically significantly greater decrease in the average 7-point SMPG profile from baseline to Week 30 (1.50 mmol/L [-27.05 mg/dL]) compared to patients in the insulin glargine group (0.60 mmol/L [10.88 mg/dL]; difference: -0.90 mmol/L [-16.16 mg/dL], p<0.0001). The 7-point SMPG profiles showed that values at all Week 30 time points were notably reduced from baseline and lower in the FRC group compared to the insulin glargine group (except for the similar pre-breakfast values).

The percentage of patients reaching HbA1c <7% with no body weight gain at Week 30 was statistically significantly higher in the FRC group (34.2%) than in the insulin glargine group (13.4%; response rate difference: 20.82%, p<0.0001). The percentage of patients reaching HbA1c <7% at Week 30 with no documented symptomatic hypoglycemia during the 30 week treatment period was markedly higher in FRC group (31.7%) than in the insulin glargine group (18.6%); the difference between the treatment groups was 13.22% (95% CI: 7.12%, 19.32%; excluding 0). The percentage of patients reaching HbA1c <7% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia during the 30 week treatment period was markedly higher in FRC group (19.9%) than in the insulin glargine group (9.0%) with a difference of 10.94% (95% CI: 5.93%, 15.96%).

The increase in the daily insulin glargine dose from baseline to Week 30 was similar between the FRC group (10.6 U) and the insulin glargine group (10.9 U; treatment difference: -0.26 U, p=0.7362). Mean daily doses at Week 30 were similar between the treatment groups at approximately 47 U. The majority of patients in both treatment groups had a final daily insulin dose >40 and ≤60 U. At Week 30, in the FRC group, the mean (SD) dose of the lixisenatide component was 16.87 µg/day (3.22), and the majority of patients (68.8%) had a final dose ≥15 to ≤20 µg.

Patients in both groups had an initial mean FPG decrease from approximately 8.0 mmol/L (143.9 mg/dL) at screening to approximately 7.3 mmol/L (132.0 mg/dL) at baseline (post-run-in). From this baseline level, similar mean FPG levels between groups were reached at Week 30 (6.78 mmol/L [122.1 mg/dL] in the FRC and 6.69 mmol/L [120.5 mg/dL] in the insulin glargine group). These findings support a well conducted and comparable titration in both groups.

The percentage of patients requiring rescue therapy in the FRC group (2.7%) was approximately half compared to the insulin glargine group (6.0%), with a risk difference between the treatment groups of -3.35% (95% CI: 6.33%, 0.36%; excluding 0).

Patient reported outcomes:

An improvement in patient reported outcomes, as measured by TRIM-D and EQ-5D-3L (VAS) and was seen in both treatment group at Week 30. Greater improvements were seen in the FRC group compared to the insulin glargine group in the TRIM-D diabetes management domain score and the EQ-5D-3L (VAS). The IWQoL-Lite total score improved in the FRC group at Week 30 while it remained almost unchanged in the insulin glargine group. Based on both patient- and investigator-rated global treatment effectiveness, at least marked improvement of diabetes was achieved by a higher percentage of patients in the FRC

group compared to the insulin glargine group, including more patients in the FRC group reporting complete control of their (patient rated: 30.0% in the FRC group versus 20.1% in the insulin glargine group; investigator-rated: 27.0% in the FRC group versus 19.7% in the insulin glargine group.

Safety results:

Overall, FRC was well tolerated and the safety profile of the FRC group reflected those of its individual components.

The median treatment duration was similar between the 2 treatment groups (211.0 days in the FRC group and 210.0 days in the insulin glargine group).

At least 1 event of documented (plasma glucose ≤70 mg/dL [3.9 mmol/L]) symptomatic hypoglycemia was reported for a similar percentage of patients: 40.0% in the FRC group and 42.5% in the insulin glargine group. The number of events per patient year was lower in the FRC group compared to the insulin glargine group (3.03 versus 4.22). Severe symptomatic hypoglycemia events were reported by 4 patients (1.1%) in the FRC group (5 events) and 1 patient (0.3%) in the insulin glargine group (1 event). Of these, 3 patients in the FRC group had alternative etiologies that may have contributed to the episodes of severe hypoglycemia.

A total of 195 patients (53.4%) in the FRC group and 191 patients (52.3%) in the insulin glargine group reported at least 1 TEAE.

Three patients experienced at least 1 TEAE leading to death: 1 patient in the FRC group (pneumonia) and 2 patients in the insulin glargine group (gallbladder cancer and cardiopulmonary failure). None of the TEAEs leading to death were considered to be possibly related to IMP.

Serious TEAEs were reported by similar percentages of patients in both treatment groups: 20 patients (5.5%) in FRC group and 18 patients (4.9%) in the insulin glargine group. There were no relevant differences regarding the pattern of serious TEAEs.

The percentage of patients who permanently discontinued IMP due to a TEAE was low overall with 10 patients (2.7%) in the FRC group and 3 patients (0.8%) in the insulin glargine group; 4 patients (1.1%) of patients in the FRC group versus none in the insulin glargine group discontinued due to TEAEs in the gastrointestinal disorder system organ class (SOC).

The most commonly reported TEAEs in the FRC group were nausea (38 patients [10.4%] versus 2 patients [0.5%] in the insulin glargine group), nasopharyngitis (32 patients [8.8%] of patients in both treatment groups), and headache (21 patients [5.8%] versus 10 patients [2.7%] in the insulin glargine group). A higher incidence of TEAEs in the gastrointestinal disorders SOC was reported in the FRC group compared to the insulin glargine group (17.0% versus 7.9%), with nausea (10.4% versus 0.5%), diarrhea (4.4% versus 2.7%), and vomiting (3.6% versus 0.5%) being the most common events in this SOC.

The incidence of any injection site reactions was low with 2 patients (0.5%, both in the insulin glargine group) reporting an event. None of these reactions were considered serious or led to permanent IMP discontinuation.

One event of allergic rhinitis reported by a patient in the insulin glargine group was adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee (not related to the IMP). No events in the FRC group were adjudicated as an allergic reaction.

No events reported on the AE form for increased lipase and/or amylase >2 x ULN were positively adjudicated as pancreatitis by the Pancreatic Safety Assessment Committee. In addition, no pancreatic neoplasms were reported in the study.

Major cardiovascular events positively adjudicated by the Cardiovascular Events Adjudication Committee were reported for 5 patients (1.4%) in the FRC group and 4 patients (1.1%) in the insulin glargine group.

Two patients in the insulin glargine group reported a TEAE of increased calcitonin (≥20 pg/mL confirmed by a repeat measurement) versus none in FRC group.

During the on-treatment period, the percentage of patients with events reported on the pen-related questionnaire was similar between the treatment groups: 11 patients (3.0%) in the FRC group and 15 patients (4.1%) in the insulin glargine group. None of the events were associated with a clinical event (ie, symptomatic hypoglycemic event, hyperglycemic AE, or any other AE).

One patient (0.3%) in the FRC group and 2 patients (0.5%) in the insulin glargine group experienced an AE of ALT increase during the on-treatment period. None were considered to be possibly related to IMP by the Investigator or met the definition for Hy's law.

No symptomatic overdose with IMP or NIMP was reported during the open-label treatment period in either treatment group.

There was 1 pregnancy (in the insulin glargine group) reported during the treatment period. The patient gave birth to a healthy baby girl by programmed cesarean.

After 30 weeks of treatment, the percentage of AIA-positive patients increased to the same degree in the FRC group and the insulin glargine group. The presence of lixisenatide had an impact neither on the titer of the AIAs nor on their cross-reactivity to human insulin indicating that the combination shows a similar immunogenicity profile to those of the individual components.

After 30 weeks of treatment with the FRC, the percentage of ADA positive patients increased, with only a small percentage of patients having quantifiable ADA concentrations.

Generally, there was no substantial difference in the TEAE profile between the antibody-positive and antibody-negative populations. There were no indications of an impact of antibody status on injection site reactions or allergic reactions.

Pharmacokinetic results:

In patients treated with the FRC who were ADA negative at baseline and Week 30, the median post-dose total lixisenatide concentrations increased from baseline to Week 30 (from 22.25 pg/mL to 57.10 pg/mL) due to the increase in dose. In patients treated with the FRC who were ADA positive at Week 30, the increase in median post-dose lixisenatide concentrations from baseline (below the lower limit of quantification in the 1 ADA positive patient for which it was measured) to Week 30 (568.00 pg/mL) was more pronounced as compared to ADA negative patients at Week 30.

Median post-dose active concentrations of lixisenatide increased from baseline to Week 30 irrespective of the ADA status at Week 30 (from 54.00 pg/mL to 181.40 pg/mL in ADA negative patients and from no available values to 277.70 pg/mL in ADA positive patients). At Week 30, the ADA status had little effect on the post-dose median active concentrations. The median post-dose active fraction decreased from baseline to Week 30 in patients who were ADA positive at Week 30, indicating the presence of lixisenatide binding ADAs.

In summary, the PK behavior of lixisenatide when administered as FRC is in line with the PK behavior of lixisenatide as observed in the lixisenatide monotherapy program.

Issue date: 26-Jan-2017