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Sponsor: Sanofi **Drug substance(s):** HOE901/AVE0010	**Study Identifiers:** U1111-1148-4334, NCT02058147 & 2013-003131-30 **Study code:** EFC12404

Title of the study: A randomized, 30-week, active-controlled, open-label, 3-treatment arm, parallel-group multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone and to lixisenatide alone on top of metformin in patients with Type 2 diabetes mellitus (T2DM)

Study center(s): Multicenter (240 centers in 23 countries).

Study period:

Date first patient enrolled: 12/Feb/2014

Date last patient completed: 17/Jun/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 lixisenatide in glycosylated hemoglobin A1c (HbA1c) change from baseline to Week 30
- To demonstrate the non-inferiority of the FRC to insulin glargine in HbA1c change from baseline to Week 30
  If noninferiority was shown, statistical superiority of the FRC compared to insulin glargine on HbA1c change from baseline to Week 30 was to be tested according to a prespecified testing hierarchy.

Secondary objectives:

- To assess the effects of the FRC versus insulin glargine alone and lixisenatide alone over 30 weeks on:
  - Percentage of patients reaching HbA1c targets
  - Glycemic control in relation to a meal as evaluated by glucose excursion and 2-hour postprandial plasma glucose (PPG) during a standardized meal test
  - Body weight
  - Fasting plasma glucose (FPG)
  - 7-point self-monitored plasma glucose profile (SMPG)
  - Percentage of patients reaching HbA1c targets with no body weight gain and/or documented symptomatic hypoglycemia
  - Insulin glargine dose (in the FRC group and insulin glargine group)
- To assess the safety and tolerability in each treatment group.
- To assess the development of anti-insulin glargine antibodies (AIAs) and/or anti-lixisenatide antibodies (ADAs)
- To assess the total and active plasma concentrations of lixisenatide following first injection of the investigational medicinal product and prior to injection as well as following injection at the end of the treatment period
- To assess the treatment effects of each treatment group on patient reported outcomes (PROs) measured by the following questionnaires:
  - Treatment Related Impact Measure-Diabetes (TRIM-D) questionnaire
  - EuroQol-5 Dimensions version 3L (EQ-5D-3L) questionnaire
  - Impact of Weight on Quality of Life-Lite (IWQoL-Lite) questionnaire
- 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, 2:2:1 randomized, active-controlled, 3-group, 30-week treatment duration, parallel group multinational and multicenter study. Randomization was stratified by values of HbA1c at Visit 4 (Week -1) (<8%, ≥8%) and second oral anti-diabetic (OAD) use at screening (yes, no).

The study comprised 3 periods:

- An up to 6-week screening period (including an up to 2-week screening phase and a 4-week run-in phase where sulfonylurea (SU), glinide, sodium glucose co-transporter-2 (SGLT-2) inhibitor, or dipeptidyl peptidase-4 (DPP-4) inhibitor if previously taken were discontinued and metformin treatment optimized up to a daily dose of at least 2000 mg or the maximal tolerated dose (≥1500 mg/day)
- A 30-week open-label randomized treatment period
- A 3-day posttreatment safety follow-up period

Number of patients**:**	Planned: 1125 (FRC: 450, insulin glargine: 450, lixisenatide: 225)
	Randomized: 1170 (FRC: 469, insulin glargine: 467, lixisenatide: 234)
	Treated: 1169 (FRC: 469, insulin glargine: 467, lixisenatide: 233)
Evaluated:	
	Efficacy: 1167 (FRC: 468, insulin glargine: 466, lixisenatide: 233)
	Safety: 1169 (FRC: 469, insulin glargine: 467, lixisenatide: 233)
	Pharmacokinetics: 688 (FRC: 466, lixisenatide: 222)

Diagnosis and criteria for inclusion: Inclusion criteria: Patients with T2DM diagnosed for at least 1 year before the screening visit, treated for at least 3 months prior to Visit 1 with metformin alone or metformin and a second OAD treatment that could be a SU, a glinide, a SGLT-2 inhibitor, or a DPP-4 inhibitor, and who were not adequately controlled with this treatment. Key exclusion criteria at screening: HbA1c <7.5% or >10.0% for patients previously treated with metformin alone; HbA1c <7.0% or >9.0% for patients previously treated with metformin and a second OAD treatment; Body Mass Index (BMI) ≤20 kg/m2 or >40 kg/m2.

Study treatments

Investigational medicinal product(s): Test drug: Insulin glargine/lixisenatide fixed ratio combination; control drugs: Insulin glargine (Lantus®, 100 U/mL) and lixisenatide

Formulation:

Insulin glargine/ lixisenatide fixed ratio combination

The FRC was supplied as a sterile aqueous solution in a prefilled disposable SoloStar® pen-injector.

Two pens (A and B) with different fixed ratios were available to allow insulin glargine titration over a range of 10 U to 60 U/day while limiting the lixisenatide dose to a maximum of 20 µg/day:

- Pen A contained 100 U/mL insulin glargine (Lantus, 100 U/mL) and 50 µg/mL of lixisenatide in a ratio of 2 U:1 µg, so that each U of insulin glargine (Lantus, 100 U/mL) is given with 0.5 µg of lixisenatide. Doses could be set from 10 U to 40 U in steps of 1 U, allowing administration of daily FRC doses between 10 U/5 µg and 40 U/20 µg.
- Pen B contained 100 U/mL insulin glargine (Lantus, 100 U/mL) and 33 µg/mL lixisenatide in a ratio of 3 U:1 µg, so that each U of insulin glargine (Lantus, 100 U/mL) is given with approximately 0.33 µg of lixisenatide. Doses could be set from 30 U to 60 U in steps of 1 U, allowing administration of daily FRC doses between 30 U/10 µg and 60 U/20 µg.

The maximum daily dose was 60 U (60 U insulin glargine and 20 µg lixisenatide).

Insulin glargine

Insulin glargine was supplied as a sterile aqueous solution in a prefilled disposable Lantus® SoloStar® pen-injector (100 U/mL). Doses could be set from 1 U to 80 U in steps of 1 U. However, in this study the maximum insulin glargine daily dose allowed was 60 U.

Lixisenatide

Lixisenatide was supplied as a disposable prefilled pen (lixisenatide pen):

- 10 µg initiation dose: disposable pen-injector device containing 3 mL of a sterile aqueous solution with 150 µg of the active ingredient (50 µg/mL)
- 20 µg maintenance dose: disposable pen-injector device containing 3 mL of a sterile aqueous solution with 300 µg of the active ingredient (100 µg/mL)

Route(s) of administration: Self-administered, subcutaneous injection for all IMPs.

Dose regimen:

Insulin glargine/lixisenatide fixed ratio combination

The FRC was self-administered once daily in the morning, in the hour (0 to 60 minutes) before breakfast. Treatment was initiated with Pen A at a daily dose of 10 U of insulin glargine/ 5 µg of lixisenatide.

Insulin glargine

Insulin glargine was self-administered once daily at any time of the day but at about the same time every day. The initial daily dose of insulin glargine during the first week of treatment was 10 U.

Dose adjustment (fixed ratio combination and insulin glargine)

The same dose adjustment algorithm was recommended for the FRC and insulin glargine and was based on patient's need for insulin. After the first week, the insulin glargine dose was titrated once a week to reach and maintain a target fasting self-monitored plasma glucose (SMPG) of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) while avoiding hypoglycemia.

In the FRC group, Pen A was to be used for total daily insulin glargine doses between 10 U and 40 U/day, and Pen B was to be used for total daily doses between 41 U and 60 U/day.

Lixisenatide

Lixisenatide was self-administered once daily in the hour (0 to 60 minutes) before breakfast or the evening meal. Lixisenatide started with once daily injections of 10 µg for 2 weeks, and then was continued with the maintenance dose of 20 µg once daily from Week 2 up to the end of the treatment period.

Noninvestigational medicinal products: Background treatment with metformin and rescue therapy

Metformin:

Metformin tablets were administered orally according to its locally approved label. Metformin was a mandatory background therapy. If previously taken, oral antidiabetic treatments other than metformin were discontinued from Visit 2. Patients in all 3 treatment groups continued metformin during the study. Daily metformin dose was increased weekly during the run-in phase by increments of up to 500 mg to a final daily dose of at least 2000 mg or up to the maximal tolerated dose, which had to be ≥1500 mg/day to allow randomization. After randomization (during the treatment period), this dose was maintained until the end of the study unless there was a specific safety issue related to this treatment.

Rescue therapy:

Routine measurements and central lab alerts were set up to ensure that glycemic parameters remained under threshold values predefined for rescue therapy. If values were above these thresholds, and no explanations were found, or appropriate actions failed, or a a daily FRC dose >60 U/20 µg dose or an insulin glargine dose >60 U was necessary to decrease glycemic parameters below the threshold values, a rescue therapy was to be introduced along with investigational medicinal product (IMP) and metformin.

Duration of treatment: Up to 30 weeks

Duration of observation: Up to 37 weeks (up to 6-week screening period + 30-week randomized treatment period + 3-day post treatment safety follow-up period)

Criteria for evaluation:

Efficacy:

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

Secondary efficacy endpoints:

- Percentage of patients with HbA1c <7% or ≤6.5% at Week 30
- Change from baseline to Week 30 in 2-hour glucose excursions and 2-hour postprandial plasma glucose (PPG) measured during a standardized meal test, 30-minute and 1-hour glucose excursions and PPG
- Body weight
- Fasting plasma glucose
- Average 7-point SMPG
- 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 ≤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 no documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L]) during the treatment period
- Insulin glargine dose at Week 30
- Percentage of patients requiring rescue therapy

Patient reported outcomes:

Treatment Related Impact Measure-Diabetes scores (total and domain scores), EQ-5D-3L variables (single utility indices and perceived health status on VAS), IWQoL-Lite scores (total and domain scores), patient- and physician-rated global treatment effectiveness evaluation scale (responses to each question)

Safety:

- Symptomatic hypoglycemia
  - Documented: typical symptoms of hypoglycemia with a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L)
  - Severe: event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
  - Probable: symptoms of hypoglycemia without plasma glucose determination, but presumably caused by a plasma glucose ≤70 mg/dL (3.9 mmol/L)

- Deaths, treatment-emergent adverse events (TEAE): serious TEAEs, TEAEs leading to treatment discontinuation, adverse events of special interest (ie, alanine aminotransferase [ALT] increase, pregnancy, symptomatic overdose with IMP/noninvestigational medicinal product [NIMP]), local intolerability at injection site, suspected allergic reactions, pancreatic events (increased amylase/lipase >2 x ULN confirmed by a repeat measurement, pancreatitis, pancreatic neoplasm), major cardiovascular events, events of increased calcitonin ≥20 pg/mL (5.9 pmol/L) confirmed by a repeat measurement, pen-related events
- Safety laboratory data: Hematology, clinical chemistry (including lipase/amylase and calcitonin), urine analysis
- Physical examinations and vital signs
- Electrocardiograms
- Immunogenicity: Anti-insulin antibody (AIA) status, titer, and cross-reactivity with human insulin for AIA positive patients; anti-drug antibody (ADA) status and concentration

Pharmacokinetics:

Total and active plasma concentrations of lixisenatide (FRC group and lixisenatide group)

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Three blood samples were taken from patients in the FRC group and patients from the lixisenatide group injecting IMP in the morning: 1 to 4 hours after IMP injection at Day 1 (Visit 5), as well as prior to IMP injection and 1 to 4 hours after IMP injection at the end of-treatment visit (Week 30).

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

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

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 of 1.1%, a true difference between FRC and the insulin glargine alone of zero and a non-inferiority margin of 0.3%, a 0.4% mean difference between FRC and lixisenatide alone in change from baseline in HbA1c, and a t-test at a 1-sided 2.5% significance level with at least 95% power. Based on the above assumptions, 1125 patients (FRC: 450, insulin glargine: 450, lixisenatide: 225) were needed for this study.

Efficacy analysis was based on the 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 postbaseline assessment of any primary or secondary efficacy endpoints.

The primary efficacy endpoint was analyzed using a mixed-effect model with repeated measures (MMRM). The MMRM model included the treatment groups, randomization strata, visit, treatment-by-visit interaction, and country as fixed-effects, 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 differences and the 95% confidence intervals (CIs) 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 including 30-week completers, ANCOVA applying multiple imputations for missing values at Week 30, 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 for HbA1c as the time from the first injection of open-label IMP up to 14 days after the last injection of IMP or up to the introduction of rescue therapy, whichever was the earliest). Treatment effects across subgroups (race, ethnicity, age group, gender, baseline BMI, baseline HbA1c, OAD use other than metformin at screening, country) were estimated for the primary endpoint using a similar MMRM model as described above (additionally including subgroup, treatment-by-subgroup, visit-by-subgroup, treatment-by-visit-by-subgroup as fixed effects).

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

A step-down testing procedure was applied to control the type I error. Once the co-primary hypotheses of statistical superiority FRC to lixisenatide alone and the non-inferiority of FRC to insulin glargine alone were both established for the primary efficacy endpoint, testing was performed according to the following order: 2-hour glucose excursion and body weight compared to insulin glargine, FPG and daily average of the 7-point SMPG compared to lixisenatide, percentage of patients reaching HbA1c <7% with no body weight gain, HbA1c (superiority test), daily average of the 7-point SMPG, percentage of patients reaching HbA1c <7% with no body weight gain and no documented symptomatic hypoglycemia, insulin glargine dose, and FPG compared to insulin glargine. When a test was not statistically significant at the 5% level, the testing procedure was stopped.

Patient reported outcomes were analyzed using the MMRM method and/or descriptive statistics.

Safety analysis was based on the safety population which consisted of all randomized patients who received at least 1 dose of IMP. All safety analyses were descriptive.

Pharmacokinetic (PK) analyses were based on the PK population which consisted of all randomized and treated patients who contributed at least 1 valid plasma analysis of lixisenatide. All PK analyses were descriptive.

Summary:

Population characteristics:

A total of 1170 patients were randomized to 1 of the 3 treatment groups (469 in the insulin glargine/lixisenatide fixed ratio combination group, 467 in the insulin glargine group and 234 in the lixisenatide group). One patient randomized to the lixisenatide group was not exposed to the study treatment (patient's request) and 3 randomized patients (1 in each treatment group) were not included in the mITT population due to a lack of post baseline efficacy data.

Demographics and baseline characteristics were generally similar across the 3 treatment groups. The median age was 59.0 years, the mean diabetes duration was 9 years and the mean BMI was 32 kg/m2. The study population was primarily Caucasian (90.1%), and 50.6% of the population were male patients.

Efficacy results:

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

Primary efficacy endpoint:

The primary objectives of the study were met as the non-inferiority and then statistical superiority (according to the prespecified testing hierarchy of the FRC) compared to insulin glargine on HbA1c change from baseline to Week 30 was demonstrated as well as statistical superiority of the FRC over lixisenatide.

From similar baseline levels of approximately 8.1%, the changes from baseline in HbA1c to Week 30 were -1.63% for the FRC group, -1.34% for the insulin glargine group, and -0.85% for the lixisenatide group, reaching mean HbA1c values of 6.50%, 6.81%, and 7.31% at Week 30, respectively.

Superiority of the FRC over lixisenatide alone was demonstrated (difference -0.78%; 95% CI: -0.898%, -0.665%; p<0.0001). The non-inferiority of the FRC compared to insulin glargine alone was demonstrated, as the upper bound of the 2-sided 95% CI of the difference was less than the predefined non-inferiority margin of 0.3% (difference -0.29%; 95% CI: -0.384%, -0.194%).

Statistical superiority of the FRC over insulin glargine alone was demonstrated for the primary efficacy endpoint based on the step down testing procedure (p<0.0001).

These results were robust across various sensitivity and subgroup analyses.

Secondary efficacy endpoints:

A markedly higher proportion of FRC-treated patients reached the prespecified HbA1c target <7% versus patients in the insulin glargine group and the lixisenatide group (respectively 73.7%, 59.4%, and 33.0%). The proportion difference (95% CI) was 14.31% (8.37%, 20.25%; p<0.0001) versus insulin glargine and 40.61% (33.63%, 47.59%; p<0.0001) versus lixisenatide. In addition, the proportion of patients reaching HbA1c ≤6.5% was markedly higher in the FRC group (55.8%) than in the insulin glargine group (39.5%) and the lixisenatide group (19.3%). The proportion difference (95% CI) was 16.35% (10.13%, 22.58%; p<0.0001) versus insulin glargine and 36.38% (29.81%, 42.95%; p<0.0001) versus lixisenatide.

Treatment with the FRC statistically significantly improved postprandial glycemic control after a standardized liquid breakfast meal in comparison to insulin glargine as shown by the results of change from baseline in 2-hour plasma glucose excursions (treatment difference: -2.13 mmol/L [-38.44 mg/dL]; p<0.0001). The decrease in 2-hour glucose excursion in the lixisenatide group was 3.23 mmol/L (-58.11 mg/dL; difference versus FRC: 0.91 mmol/L [16.44 mg/dL]). A greater decrease in 2-hour PPG from baseline to Week 30 during was also observed in the FRC group (-5.68 mmol/L [-102.39 mg/L]) compared to the insulin glargine group (-3.31 mmol/L [-59.55 mg/dL]) and the lixisenatide group (-4.58 mmol/L [-82.57 mg/dL]). Similar decreases as seen for 2 hour blood glucose excursions and 2-hour PPG were observed for 30-minute and 1-hour blood glucose excursions and 30 minute and 1-hour PPG.

Patients in the FRC group lost weight (-0.29 kg) from baseline to Week 30 while patients in the insulin glargine group gained weight (+1.11 kg; statistically significant difference of -1.40 kg, p<0.0001). The largest weight loss was in the lixisenatide group (- 2.30 kg).

Starting from comparable baseline levels, the reductions from baseline to Week 30 in FPG were similar between the FRC group (3.46 mmol/L [-62.39 mg/dL]) and the insulin glargine group (-3.27 mmol/L [-58.95 mg/dL]). Reductions were smaller in the lixisenatide group (-1.50 mmol/L [-27.02 mg/dL]). The difference of the FRC group versus the insulin glargine group was 0.19 mmol/L [-3.45 mg/dL] and versus the lixisenatide group it was statistically significantly greater (-1.96 mmol/L [35.38 mg/dL]; 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 (3.35 mmol/L [-60.36 mg/dL]) compared to patients in the insulin glargine group (-2.66 mmol/L [-47.87 mg/dL]; difference -0.69 mmol/L [12.49 mg/dL]) and patients in the lixisenatide group (1.95 mmol/L [-35.11 mg/dL]; difference 1.40 mmol/L [25.24 mg/dL]) (p<0.0001 for both comparisons). Seven-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 lixisenatide group and to the insulin glargine group (except for the similar prebreakfast values).

A statistically significantly higher proportion of patients reached the composite endpoint of HbA1c <7.0% with no body weight gain at Week 30 in the FRC group (43.2%) than in the insulin glargine group (25.1%); the proportion difference was 18.08% (p<0.0001). The proportion of patients reaching this composite endpoint was also markedly higher in the FRC group compared to the lixisenatide group (27.9%) and the difference was 15.22%. A higher proportion of patients reached the composite endpoint of HbA1c <7% at Week 30 with no documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L]) in the FRC group (53.6%) than in the insulin glargine group (44.4%) and the lixisenatide group (30.5%). A statistically significantly higher proportion of patients reached the triple composite endpoint of HbA1c <7.0% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L]) during the study in the FRC group (31.8%) than in the insulin glargine group (18.9%); the proportion difference was 12.98%. The proportion of patients reaching this triple composite endpoint was also numerically higher in the FRC group compared to the lixisenatide group (26.2%).

At Week 30, the mean average daily insulin glargine dose was similar between the FRC group (39. 77 U) and the insulin glargine group (40.46 U; difference: -0.69 U; p=0.4857).

In the FRC group, the mean (SD) average lixisenatide dose was 15.51 (4.06) µg at Week 30 and most patients (58.6%) had a final dose of ≥15 to ≤20 µg. In the lixisenatide group, the majority of patients (88.8%) administered a final lixisenatide dose of 20 µg.

The percentage of patients requiring rescue therapy in the FRC group (17 patients [3.6%]) was similar to the insulin glargine (capped at 60 U) group (16 patients [3.4%]) and was lower than in the lixisenatide group (29 patients [12.4%]).

Patient reported outcomes:

Starting from comparable baseline levels, TRIM-D scores and EQ-5D-3L scores improved to a similar extent in all 3 treatment groups with the exception of the TRIM-D diabetes management domain score that improved to a greater extent in the FRC group compared to the lixisenatide group (difference 3.8; 95% CI [0.95, 6.63] excluding 0).

Analysis of the patient-rated and physician-rated global treatment effectiveness evaluation scales showed that patient and physician perceptions of treatment effectiveness were generally similar between the FRC group and the insulin glargine group and less favorable in the lixisenatide group. According to both patients and physicians, most patients in the FRC group (89.1% and 86.6%) and the insulin glargine group (88.8% and 84.3%) had at least a marked improvement of their diabetes. In addition, physicians reported that a higher percentage of patients in the FRC group (35.6%) than in the insulin glargine group (26.3%) had complete control of diabetes.

Safety results:

The FRC was well tolerated during the 30-week on-treatment period; the safety profile of the FRC group reflected those of its components.

The median treatment duration was 211.0 days in all 3 treatment groups.

Similar percentages of patients in the FRC group (25.6%) and in the insulin glargine group (23.6%) reported documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L]) as per protocol definition. The number of events per patient-year was generally low and comparable between groups, 1.44 for FRC and 1.22 for insulin glargine. In the lixisenatide group the percentage of patients and the event rate per patient-year were lower (6.4%; 0.34 events per patient-year).

One event of severe symptomatic hypoglycemia was reported during the study and occurred in the insulin glargine group.

A total of 267 patients (56.9%) in the FRC group, 227 patients (48.6%) in the insulin glargine group, and 157 patients (67.4%) in the lixisenatide group reported at least 1 TEAE.

In total, 7 patients died during the study. Of these, 6 patients died due to TEAEs (2 patients in the FRC group, 3 patients in the insulin glargine group, and 1 patient in the lixisenatide group) and 1 patient in the insulin glargine group died due to a posttreatment AE. None of the fatal events were considered as related to IMP.

Serious TEAEs were reported by a similar percentage of patients in each treatment group: 18 patients (3.8%) in the FRC group, 19 patients (4.1%) in the insulin glargine group, and 9 patients (3.9%) in the lixisenatide group.

A lower percentage of patients permanently discontinued IMP due to TEAEs in the FRC group (12 patients [2.6%]) compared to the lixisenatide group (21 patients [9.0%]) whereas the percentage was similar to the insulin glargine group (9 patients [1.9%]). The difference between groups can be explained by the higher incidence of TEAEs leading to permanent treatment discontinuation in the SOC gastrointestinal disorders in the lixisenatide group (12 patients [5.2%] compared to 4 patients [0.9%] in the FRC group and 1 patient [0.2%] in the insulin glargine group). In addition, the TEAE of urticaria led to permanent IMP discontinuation of 3 patients (0.6%) in the FRC group.

In the FRC group and in the lixisenatide group, the most commonly reported TEAEs at the preferred term (PT) level were nausea (45 patients [9.6%] in the FRC group and 56 patients [24.0%] in the lixisenatide group versus 17 patients [3.6%] in the insulin glargine group) and diarrhea (42 patients [9.0%] in the FRC group and 21 patients [9.0%] in the lixisenatide group versus 20 patients [4.3%] in the insulin glargine group). The incidence of gastrointestinal side effects following initiation of the IMP was lower in the FRC group than in the lixisenatide group. The most commonly reported TEAEs in the insulin glargine group were nasopharyngitis (25 patients [5.4%]) and upper respiratory tract infection (23 patients [4.9%]).

Injection site reactions during the on-treatment period were reported by similarly low percentages of patients across the 3 treatment groups (12 patients [2.6%] in the FRC group, 8 patients [1.7%] in the insulin glargine group, and 7 patients [3.0%] in the lixisenatide group). None were considered serious. One patient in the lixisenatide group had injection site erythema that led to treatment discontinuation.

The percentages of patients with any TEAE adjudicated as allergic reaction during the on-treatment period were low and similar for the 3 treatment groups: 6 patients (1.3%) in the FRC group, 3 patients (0.6%) in the insulin glargine group, and 2 patients (0.9%) in the lixisenatide group. Three patients (0.6%) in the FRC group and 1 patient (0.4%) in the lixisenatide group had urticaria that was considered possibly related by the Allergic Reaction Assessment Committee (ARAC) and 1 patient (0.4%) in the lixisenatide group had an anaphylactic reaction that was considered possibly related by the ARAC. In addition to the 4 cases of urticaria considered as possibly related by the ARAC, there were 3 additional allergic events reported by 3 patients (0.6%) in the FRC group that were adjudicated as non-related angioedema by the ARAC. The reported diagnoses (PTs) by the Investigators for these events were: angioedema, lip swelling, and allergic oedema.

There were no cases of pancreatitis positively adjudicated by the Pancreatic Safety Assessment Committee (PSAC). No TEAEs with the PT of pancreatitis were reported by the Investigators. One case of pancreatic cancer was reported in the insulin glargine group.

The percentages of patients with any TEAE adjudicated as major cardiovascular event by the CAC were low for the 3 treatment groups: 2 patients (0.4%) in the FRC group, 7 patients (1.5%) in the insulin glargine group, and 2 patients (0.9%) in the lixisenatide group.

During the on-treatment period, 1 patient (0.2%) in the insulin glargine group reported a TEAE of increased calcitonin (≥20 pg/mL) versus none in either the FRC group or the lixisenatide group.

Pen-related events were reported in 25 patients (5.3%) in the FRC group, 10 patients (2.1%) in the insulin glargine group, and 9 patients (3.9%) in the lixisenatide group; none of the pen-related events was associated with a clinical events (ie, symptomatic hypoglycemic event, hyperglycemic AE or other AE).

During the on-treatment period, the percentages of patients with increased ALT reported on the specific AE form were low and similar for the 3 treatment groups: 1 patient (0.2%) in the FRC group, 2 patients (0.4%) in the insulin glargine group, and 1 patient (0.4%) in the lixisenatide group. None of the events met the definition for Hy's Law.

No symptomatic overdose with IMP was reported in any treatment group during the on-treatment period.

No pregnancies were reported during the study.

No particular safety issues were identified in the review of clinical laboratory parameters, vital signs, physical examination findings, or ECGs.

After 30 weeks of treatment, there was no clinically relevant imbalance in AIA positive patients between 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 FRC shows similar immunogenicity as the individual components.

After 30 weeks of treatment with the FRC or lixisenatide, the percentage of patients with ADAs increased but only a small percentage of patients had quantifiable ADA concentrations.

Generally, there was no substantial difference in the TEAE profile between the antibody-positive and antibody-negative populations. In the FRC group, 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 or lixisenatide who were ADA negative at Week 30, the median postdose lixisenatide concentrations increased from baseline to Week 30 (from 11.10 pg/mL to 54.70 pg/mL in the FRC group and from 45.05 pg/mL to 112.50 pg/mL in the lixisenatide group) due to the increase in dose. In patients treated with the FRC or lixisenatide who were ADA positive at Week 30, the increase in median postdose lixisenatide concentrations from baseline to Week 30 (from 20.40 pg/mL to 375.00 pg/mL in the FRC group and from 41.10 pg/mL to 648.00 pg/mL in the lixisenatide group) was more pronounced as compared to ADA negative patients at Week 30.

Median postdose active concentrations of lixisenatide increased from baseline to Week 30 in the FRC group (from below the LLOQ to 161.15 pg/mL in ADA negative patients and from 59.10 pg/mL to 144.65 pg/mL in ADA positive patients) and the lixisenatide group (from 105.80 pg/mL to 287.55 pg/mL in ADA negative patients and from below the LLOQ to 392.95 pg/mL in ADA positive patients) irrespective of the ADA status. At Week 30, the median active fraction decreased in ADA positive patients in both treatment groups, indicating the presence of lixisenatide binding ADAs (FRC group: from 2.830 [1 patient] to 0.500 in ADA; lixisenatide group: the median active fraction was 0.632 in ADA positive patients at Week 30 [no baseline values avialable]).

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

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