SYNOPSIS

Title of the study: ACT12374 - A randomized, 24-week, open-label, 2-arm parallel-group, multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination versus insulin glargine on top of metformin in type 2 diabetic patients
Investigator(s): [redacted]
Study center(s): Multicenter (67 centers) in 13 countries: Chile, Czech Republic, Germany, Denmark, France, Hungary, Lithuania, Mexico, Poland, Romania, Slovakia, Sweden, and United States of America.
Publications (reference): NA
Study period: Date first patient enrolled: 21-Nov-2011 Date last patient completed: 17-Dec-2012
Phase of development: Phase 2A
Objectives: Primary objective: To demonstrate the non-inferiority of insulin glargine/lixisenatide fixed ratio combination versus insulin glargine on glycemic control over 24 weeks, as evaluated by glycated hemoglobin A1c (HbA1c) reduction in type 2 diabetic patients not adequately controlled with metformin Secondary objectives: - To demonstrate the superiority of insulin glargine/lixisenatide fixed ratio combination versus insulin glargine on glycemic control in relation to a meal over 24 weeks, as evaluated by 2-hour post-prandial glucose (PPG) and glucose excursion during a standardized meal test. • To assess the efficacy of insulin glargine/ lixisenatide fixed ratio combination on: - Percentage of patients reaching HbA1c <7% or ≤6.5% at Week 24 - 7-point self-monitored plasma glucose (SMPG) profile (each time point and mean daily value) at Week 24 - Body weight at Week 24 - Insulin glargine dose at Week 24 - Fasting plasma glucose (FPG) at Week 24 - Percentage of patients requiring rescue therapy during the 24-week open label treatment period - 30-minute and 1-hour PPG and plasma glucose excursion during standardized meal test at Week 24 - Percentage of patients reaching HbA1c <7% at Week 24 with no documented symptomatic hypoglycemia during the 24-week open label treatment period - Percentage of patients reaching HbA1c <7% with no weight gain at Week 24 • To assess safety and tolerability of insulin glargine/ lixisenatide fixed ratio combination. • To assess the plasma concentration of lixisenatide (in the insulin glargine/lixisenatide fixed ratio combination group) following injection on Day 1 and at Week 24. • To assess the development of anti-lixisenatide (for insulin glargine/lixisenatide fixed ratio combination) and anti-insulin antibodies (for both treatment groups).

Methodology: This was an open-label, 1:1 randomized, active-controlled, 2-arm, 24-week duration, parallel-group study comparing:

- Insulin glargine/lixisenatide fixed ratio (2 U of insulin glargine for 1 µg of lixisenatide) combination
- Insulin glargine alone

The patients were stratified by screening values of HbA1c (<8, ≥8%) and body mass index (BMI) (<30, ≥30 kg/ m^2). The study comprised 3 periods: an up-to 2-week screening period; a 24-week randomized treatment period; a 3-day safety follow-up period.

Number of patients:	Planned: 310
	Randomized: 323
	Treated: 323
	Completed: 309
Evaluated: Efficacy:	323
	Safety: 323
	Pharmacokinetics: 161

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus diagnosed for at least 1 year, treated with metformin at a stable dose of at least 1.5 g/day for at least 3 months prior to screening visit, and with HbA1c ≥7% and ≤10% at screening.

Study treatments

Investigational medicinal product(s): Insulin glargine/lixisenatide fixed ratio combination and insulin glargine

- Formulation:
- Tested drug: Insulin glargine/lixisenatide fixed ratio combination (100 U/mL insulin glargine/50 µg/mL lixisenatide [ratio 2 U/1 µg]) was supplied as a sterile, aqueous solution in 3 mL cartridges to be used in a flexible dose re-usable pen (TactiPen®).
- Control drug: Insulin glargine was supplied as a sterile, aqueous solution in Lantus® SoloSTAR® disposable self-injector device (3 mL of 100 U/mL).

Route(s) of administration: Subcutaneous injection

Dose regimen: In both groups, the initial daily dose of insulin glargine to be administered during the first week of treatment was 10 U. Afterwards, the dose was adjusted to achieve a target fasting SMPG in the range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L). The dose was titrated weekly until the patient reached the target fasting SMPG. Thereafter, until the end of the study, the dose was adjusted as necessary to maintain a fasting SMPG between 80 and 100 mg/dL (4.4 and 5.6 mmol/L), inclusive. Doses could be reduced or modified at any time for hypoglycemia.

In the insulin glargine/lixisenatide fixed ratio combination group, the lixisenatide dose was automatically increased or decreased following insulin glargine dose increase or decrease according to the 2 U/1 µg fixed ratio used, and the maximum allowed dose of insulin glargine was 60 U (corresponding to a lixisenatide dose of 30 µg). In the insulin glargine only arm, the dose of insulin glargine administered could go higher than 60 U.

Batch number(s): [redacted]

Noninvestigational medicinal product(s) (if applicable): metformin

Formulation: Metformin ≥1.5 g/day.

Route(s) of administration: Oral

Dose regimen: Metformin was to be kept at stable dose throughout the study unless there was a specific safety issue related to this treatment.

Batch number(s): Not applicable

Duration of treatment: 24 weeks

Duration of observation: Maximum duration of approximately 27 weeks.

Criteria for evaluation:

Efficacy:

Primary Endpoint:

- Change in HbA1c from baseline to Week 24

Secondary Endpoints:

- Change in 2-hour PPG during meal test from baseline to Week 24
- Change in 2-hour plasma glucose excursion during meal test from baseline to Week 24
- Percentage of patients reaching HbA1c ≤6.5% or <7% at Week 24
- Change in 7-point SMPG profiles from baseline to Week 24 (each time point and mean daily value)
- Change in body weight from baseline to Week 24,
- Average daily Insulin glargine dose at Week 24
- Change in FPG from baseline to Week 24
- Percentage of patients requiring rescue therapy during the 24-week open-label treatment period
- Change in 30-minute and 1-hour PPG and plasma glucose excursion during meal test from baseline to Week 24
- Percentage of patients reaching HbA1c <7% at Week 24 with no documented symptomatic hypoglycemia during the 24-week open label treatment period
- Percentage of patients reaching HbA1c <7% with no weight gain at Week 24

Exploratory Endpoints:

- Percentage of patients reaching HbA1c <7% at Week 24 with no documented symptomatic hypoglycemia during the 24-week open-label treatment

Safety: Adverse events, serious adverse events, symptomatic hypoglycemia, vital signs, electrocardiogram (ECG), safety laboratory values.

Pharmacokinetics: Pharmacokinetic variables included plasma concentrations of lixisenatide for insulin glargine/lixisenatide fixed ratio combination group.

Antibody variables:

- Insulin glargine/lixisenatide fixed ratio combination group: anti-lixisenatide antibody status (positive, negative), concentration (nmol/L) and the change from baseline during the course of the clinical study.
- For both treatment groups: anti-insulin glargine antibody status (positive, negative), titer, with additional determination of cross reactivity to human insulin for anti-insulin glargine positive patients and the change from baseline during the course of the clinical study.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Blood samples for anti-insulin and anti-lixisenatide antibody determination were to be taken before injection of investigational medicinal product (IMP), at randomization visit (Visit 3) and end of treatment visit (Visit 17), in both treatment groups for anti-insulin antibody and from all patients treated with insulin glargine/lixisenatide fixed ratio combination for anti-lixisenatide antibody. Samples were also taken in case of premature discontinuation from IMP, if possible.

Anti-insulin antibodies and anti-lixisenatide antibodies were determined at centralized laboratories using validated assay methodologies (highly sensitive assay methodology for anti-lixisenatide antibodies). All plasma samples were to be analyzed using a validated enzyme linked immuno-sorbent assay (ELISA) for total lixisenatide (bound and unbound to anti-lixisenatide antibodies) with a lower limit of quantification (LLOQ) of 5.5 pg/mL.

Three blood samples were to be taken for patients from the insulin glargine/lixisenatide fixed ratio combination arm; at baseline and at end of treatment visits. One sample was to be taken immediately before IMP injection and 2 samples were to be taken in the time period from 0.5 to 2 hours and from 2.5 to 4 hours post injection. Samples were also to be taken in case of premature discontinuation from IMP, if possible.

Statistical methods:

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

The primary endpoint (change in HbA1c from baseline to Week 24) was analyzed using an analysis of covariance (ANCOVA) model with treatment (insulin glargine/lixisenatide fixed ratio combination, insulin glargine alone), randomization strata of screening HbA1c (<8%, ≥8%), randomization strata of screening BMI (<30 kg/ m^2, ≥30 kg/m^2), and country as fixed effects and using the baseline HbA1c value as a covariate.

The non-inferiority of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone was tested using a 1-sided statistical test with alpha level of 0.025 and a non-inferiority margin of 0.4% HbA1c. The non-inferiority would be demonstrated if the upper bound of the 2-sided 95% confidence interval (CI) of the difference between insulin glargine/lixisenatide fixed ratio combination and insulin glargine alone on mITT population is ≤0.4%. If non-inferiority is established, then a corresponding check of statistical superiority of insulin glargine/ lixisenatide fixed ratio combination over insulin glargine alone would be performed for the primary endpoint.

All continuous secondary efficacy endpoints were analyzed using a similar ANCOVA model with treatment, randomization strata of screening HbA1c (<8%, ≥8%), randomization strata of screening BMI (<30 kg/m^2, ≥30 kg/m^2), and country as fixed effects and using the baseline value of the corresponding parameter as a covariate. Insulin glargine dose was not included in the ANCOVA model as a covariate since patients enrolled were insulin-naïve.

All categorical secondary efficacy endpoints were analyzed by using Cochran-Mantel-Haenszel method stratified by randomization strata of screening HbA1c (<8%, ≥8%) and BMI (<30 kg/m^2, ≥30 kg/m^2).

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 evaluation of adverse events, laboratory, vital sign, and ECG data was descriptive.

Summary:

Population characteristics: A total of 323 patients were randomized to 1 of the 2 treatment groups (161 in the insulin glargine/lixisenatide fixed ratio combination group and 162 in the insulin glargine group). All randomized patients were exposed to the study treatment and were included in the mITT population. Demographics and baseline characteristics were generally similar across the treatment groups. The median age was 58 years. The study population was primarily Caucasian (98.5%) and included 20% of Hispanic patients. The percentage of patients completing the study treatment was very high in both treatment groups (93.2% for the combination group and 98.1% for the insulin glargine group).

Efficacy results: Treatment with insulin glargine/lixisenatide fixed ratio combination and insulin glargine resulted in a decrease in HbA1c from baseline to Week 24. The least squared (LS) mean changes from baseline to Week 24 in HbA1c were -1.82% for the combination group and -1.64% for the insulin glargine group reaching a mean HbA1c level of 6.3% and 6.5% at Week 24 respectively. LS mean difference between the combination group and insulin glargine group was -0.17% (95% CI; [-0.312% to -0.037%]). Based on the pre-specified primary analysis, the non-inferiority of the combination group compared to the insulin glargine group was demonstrated, as the upper bound of the 2-sided 95% CI of the LS mean difference was less than the

predefined non-inferiority margin of 0.4%.

Statistical superiority of the insulin glargine/lixisenatide fixed ratio combination over insulin glargine was also demonstrated for this primary end point (LS mean difference versus insulin glargine group = -0.17%; p-value = 0.0130).

The reduction in HbA1c at Week 24 in the respective treatment groups was similar in anti-lixisenatide antibody-positive as compared to anti-lixisenatide antibody-negative patients and in anti-insulin glargine antibody-positive as compared to anti-insulin glargine antibody-negative patients.

Treatment with insulin glargine/lixisenatide fixed ratio combination significantly improved postprandial glycemic control in comparison to insulin glargine as shown by the results for the 2-hour PPG assessment (LS mean difference of -3.17 mmol/L [-57.07 mg/dL]; p-value <0.0001) and for 2-hour glucose excursion (LS mean difference of -3.24 mmol/L [-58.43 mg/dL]; p-value <0.0001). Consistent results were observed for the 30-minute and 1-hour PPG as well as for the 30-minute and 1-hour glucose excursions with a greater reduction from baseline to Week 24 after a standardized meal in the insulin glargine/lixisenatide fixed ratio combination group than in the insulin glargine group.

Patients treated with insulin glargine/lixisenatide fixed ratio combination had a statistically significant greater decrease in average 7-point SMPG profile compared to patients treated with insulin glargine (LS mean difference of -0.30 mmol/L [-5.48 mg/dL]; p-value = 0.0154).

A statistically significant difference in the body weight change from baseline to Week 24 was found between the 2 treatment groups. Body weight decreased in the insulin glargine/lixisenatide fixed ratio combination group and increased in the insulin glargine group with a LS mean body weight change from baseline to Week 24 of -0.97 kg and +0.48 kg for each group respectively. LS mean difference for insulin glargine/lixisenatide fixed ratio combination versus insulin glargine was -1.44 kg; (95% CI: [-2.110 to -0.773]; p <0.0001.

For average daily insulin glargine dose at Week 24 the difference between insulin glargine/lixisenatide fixed ratio combination and insulin glargine treatment groups was close to statistical significance (LS mean difference of -3.24 U; (95% CI: [-6.592 to 0.114]; p = 0.0583).

Similar reductions in mean FPG from baseline to Week 24 (LS mean changes of -3.35 mmol/L [-60.32 mg/dL] in the combination group and of -3.51 mmol/L [-63.28 mg/mL] in the insulin glargine group) were observed. Only 1 patient (in the insulin glargine group) required rescue therapy.

A slightly higher percentage of patients reached an HbA1c <7% at Week 24 with no documented symptomatic hypoglycemia (plasma glucose concentration ≤3.9 mmol/L [70 mg/dL]) in the combination group (67.5% versus 59%; response rate difference between the treatment groups was 8.5% (95% CI: [-1.90% to 18.94%]).

Significantly more patients treated with the combination reached the 2 composite endpoints of HbA1c <7% with no weight gain at Week 24 (56.3% versus 37.3% ; response rates difference between the treatment groups were 19% (95% CI: [8.57% to 29.51%]) and HbA1c <7% with no weight gain at Week 24 and no documented symptomatic hypoglycemia (plasma glucose concentration ≤70 mg/dL [3.9 mmol/L]) (46.3% versus 28.6%; response rates difference between the treatment groups were 17.7% (95% CI: [7.46% to 27.97%]).

Safety results:

Insulin glargine/lixisenatide fixed ratio combination was overall well tolerated. Slightly more patients in the insulin glargine/lixisenatide fixed ratio combination group (86 [53.4%]) reported treatment-emergent adverse events (TEAEs) than in the insulin glargine group (82 [50.6%]). The most frequently reported TEAE in the combination group was nausea (12 [7.5%] versus 0 in the insulin glargine group).

Forty (24.8%) patients treated with the combination had 81 symptomatic hypoglycemia events (including documented, severe, and probable symptomatic hypoglycemia) as compared to 40 (24.7%) patients with 84 events in the insulin glargine group. The number of events per patient-year in symptomatic hypoglycemia was 1.11 in both treatment groups. No severe symptomatic hypoglycemia was reported. For documented symptomatic hypoglycemia with plasma glucose ≤70 mg/dL (3.9 mmol/L), the number and percentage of patients as well as the number of events were similar in both treatment groups: 35 [21.7%] patients and 71 events in the combination group versus 37 [22.8%] patients and 79 events in the insulin glargine group.

In the insulin glargine/lixisenatide fixed ratio combination group, the percentage of patients with symptomatic hypoglycemia was 21.3% (16 of 75 patients) in anti-lixisenatide antibody-positive patients and 27.8% (22 of 79 patients) in anti-lixisenatide antibody-negative patients during the on-treatment period.

In the insulin glargine/lixisenatide fixed ratio combination group, the percentage of patients with symptomatic hypoglycemia was 19.7% (13 of 66 patients) in insulin glargine antibody-positive patients and 28.1% (25 of 89 patients) in insulin glargine antibody-negative patients. In the insulin glargine group, the percentage of patients with symptomatic hypoglycemia was 21.6% (11 of 51 patients) in insulin glargine antibody-positive patients and 25.2% (26 of 103 patients) in insulin glargine antibody-negative patients.

Fifteen patients (9 [5.6%] for the combination group and 6 [3.7%] for the insulin glargine group) had treatment-emergent serious adverse events which were distributed over a variety of system organ classes (SOCs) without a notable increase in any specific SOC.

The percentage of patients completing the study was very high in both treatment groups (93.2% for the combination group and 98.1% for the insulin glargine group). Six patients treated with the combination and none receiving insulin glargine had TEAEs leading to treatment discontinuation: 1 patient had ovarian cancer, 1 patient had an allergic reaction (preferred term (PT): hypersensitivity, adjudicated as no allergic reaction by the ARAC), 1 patient had headaches, and 1 dizziness. Finally, 2 patients discontinued the treatment due to gastrointestinal disorders, 1 with PTs of nausea and vomiting and 1 with PT of nausea only.

No death was reported in this study.

A total of 2 patients (1 [0.6%] in each group) reported 6 events adjudicated as allergic reactions by the Allergic Reaction Assessment Committee (ARAC) all with the same diagnosis of allergic rhinitis. None was adjudicated as possibly related to the IMP. A total of 5 (3.1%) patients in the combination group and 1 (0.6%) in the insulin glargine group experienced injection site reactions. None of them was considered serious or severe or lead to treatment discontinuation.

Six events from 4 patients were reported in the CV specific form in e-case report form by investigators and sent to the Cardiovascular Events Adjudication Committee (CAC) for adjudication. Of these, a percutaneous coronary intervention in 1 patient for the combination treated group was adjudicated as a percutaneous coronary intervention (PCI) by the CAC. Additionally, for the insulin glargine group, an event of ECG signs of myocardial ischemia was adjudicated as hospitalization for unstable angina by the CAC and, in the same patient, an event of coronary revascularization procedure was adjudicated as a PCI by the CAC.

No TEAE of pancreatitis (elevation of amylase and/or lipase >2 x upper limit of normal (ULN) with clinical signs and/or symptoms with confirmed diagnosis) or increased calcitonin $\geq$20 pg/mL was reported in the study.

Five patients (4 patients [2.5%] in the combination treatment group and 1 patient [0.6%] in the insulin glargine group) with elevated lipase (≥3 x ULN) but no relevant symptoms were observed.

One patient from the insulin glargine group had elevated amylase (≥3 x ULN).

The vital signs data and the assessment of ECG readings did not reveal any specific safety signal.

After 24 weeks of treatment with the insulin glargine/lixisenatide fixed ratio combination, 49.0% of the patients were anti-lixisenatide antibody-positive. For the majority of antibody-positive patients, antibody concentration was <LLOQ.

After 24 weeks of treatment, the percentage of anti-insulin glargine antibody-positive patients (42.6% versus 32.9%, respectively) and the mean titer (4 versus 2, respectively) were higher in the combination group compared to the insulin glargine group. However, due to the limited number of patients, any conclusion on the relevance of the differences cannot be drawn.

Overall there was no substantial difference in the TEAE profile between the antibody positive and the antibody negative populations.

Pharmacokinetic results:

In patients of the insulin glargine/lixisenatide fixed ratio combination group who were anti-lixisenatide antibody-negative, less than one-third (22 out of 72 patients) had pre-injection concentrations above the LLOQ at Week 24 (median: LLOQ). The median post-injection concentrations of lixisenatide at Week 24 were 59.4 and 78.9 pg/mL in the time frames >0 to ≤2 hours and >2 to ≤4 hours, respectively. In antibody-positive patients, the concentrations were markedly higher at Week 24 due to the presence of antibodies with median values of 401.5 pg/mL (pre-injection), and 513 and 575 pg/mL in the time frames >0 to ≤2 hours and >2 to ≤4 hours (post-injection), respectively.

Conclusions: [redacted]

Date of report: 19-Nov-2013