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Sponsor: Sanofi	**Study Identifiers:** U1111-1200-1162, NCT03529123
Drug substance(s): Insulin Glargine / Lixisenatide	**Study code:** INSLIL08556

Title of the study: A randomized, 24-week, controlled, open label, parallel arm, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination (FRC) to insulin glargine in type 2 diabetes patients, inadequately controlled on Basal Insulin with or without Metformin (INSLIL08556)

Study center(s): 13 sites across India all with at least 1 patient randomized

Study period:

Date first patient enrolled: 19/Jun/2018

Date last patient completed: 27/Nov/2019

Phase of development: Phase 3

Objectives:

Primary objective:

To demonstrate the superiority of the FRC to insulin glargine in HbA1c change from baseline to Week 24.

Secondary objectives:

1. To assess the effects of the FRC in comparison with insulin glargine over 24 weeks on:
   a) Percentage of patients reaching HbA1c targets (<7%)
   b) Glycemic control in relation to a meal as evaluated by 2-hour Post-prandial Plasma Glucose (PPG)
   c) Body weight,
   d) Fasting Plasma Glucose (FPG).
   e) Percentage of patients reaching HbA1c targets of <7% with no body weight gain and no hypoglycemia (as defined in the evaluation criteria).
   f) 7-point Self-Monitoring Plasma Glucose (SMPG) profile
   g) Insulin glargine dose.
2. To assess the safety and tolerability in each treatment group

Methodology:

This study was an open-label, 1:1 randomized, active-controlled, 2-arm, 24-week treatment duration, parallel-group, multicenter study comparing the FRC to insulin glargine. The randomization was stratified by value of HbA1c at Visit 5 (Week -1), (<8%, ≥8%) and whether or not patients used metformin at screening. This was an outpatient study consisting of 10 on-site visits and 10 phone-call visits. The total study duration for each patient was 33 weeks, which comprised of 3 periods:

1. Screening – up to 8 weeks
   a) An up to 2-week screening phase – visits 1 and 2. This was conducted over study weeks -8 and -7. Run-in visit (visit 2) could be performed less than 2 weeks after screening visit if the laboratory data were available.

b) A 6-week run-in phase – visits 2, 3, 4 and 5. This was conducted over study weeks -6 to -1. At visit 2, patients not already on insulin glargine treatment switched to it (stopped all other anti-diabetic medications except metformin) and those already being treated with insulin glargine had their doses titration/stabilization performed. If on metformin, patients were allowed to continue with it and other OADs if previously taken at visit 2 were discontinued.

2. A 24-week open-label randomized treatment period – visits 6 to 19. This was conducted over study weeks 1 to 24.

3. A 3-day post-treatment safety follow-up period – visit 20. This was conducted for safety follow-up, 3 days after the completion of the last study treatment, regardless of status of completion of all the doses required by the study.

Number of patients: Planned: 254 patients (127 per treatment arm)

Randomized: 248 (FRC: 125; Insulin glargine: 123)

Evaluated:

Efficacy (per protocol population): 242 (FRC: 121; Insulin glargine: 121)

Safety: 247 (FRC: 124; Insulin glargine: 123)

Diagnosis and criteria for inclusion:

Consenting patients aged ≥18 years and <65 years with type 2 diabetes mellitus (T2DM) diagnosed at least 1 year before screening, and HbA1c ≥ 7.5% or ≤ 10%; FPG ≤180 mg/dL (if on basal insulin + 2 OADs or with 1 OAD other than metformin) and FPG ≤200 mg/dL (if on basal insulin only or basal insulin + metformin) were eligible to enroll. The patients were required to have treatment with a basal insulin for at least 6 months, with a stable regimen for at least 3 months before the screening visit, with stable dose of 15-40 U for at least 2 months (fluctuations limited to ± 20%). The permitted OADs (up to 2 OADs) along with the basal insulin treatment were, also required to be at a stable regimen: a metformin (≥ 1000mg/day or maximal tolerated dose), a sulfonylurea (SU), a glinide, a dipeptidyl-peptidase-4 inhibitor (DPP-4 inhibitor), an alpha-glucosidase inhibitors (AGI) or a thiazolidinedione. The qualifying BMI range required was ≥ 19 kg/m^2 and ≤ 40 kg/m^2 at screening visit.

Patients who complete their run-in period were randomized if they had HbA1c ≥ 7% or ≤ 10% at visit 5-week -1 and their mean fasting self-monitored plasma glucose (FSMPG) was ≤140 mg/dL (minimum of 4 self-measurements in the week preceding randomization visit).

Study treatments

Investigational medicinal products: FRC (tested drug) and insulin glargine (Lantus®, control drug)

Formulation:

SOLIQUA/ 2:1 and 3:1 Insulin Glargine/Lixisenatide fixed ratio combination (FRC)

The FRC was supplied as a sterile aqueous solution in a pre-filled disposable SoloStar pen injector. Two pens (peach and olive) with different insulin glargine/lixisenatide 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:

- Peach pen (2:1) contained 3 mL of sterile solution with 100 U/mL insulin glargine and 50 µg/mL lixisenatide in a ratio of 2 U insulin glargine/1 µg lixisenatide, so that each unit of insulin glargine was given with 0.5 µg of lixisenatide. The pen was used to deliver FRC doses from 10 U (10 U/5 µg) to 40 U (40 U/20 µg) in steps of 1 unit.
- Olive pen (3:1) contained 3 mL of sterile solution with 100 U/mL insulin glargine and 33 µg/mL lixisenatide in a ratio of 3 U insulin glargine/1 µg lixisenatide, so that each unit of insulin glargine was given with 0.33 µg of lixisenatide. The pen was used to deliver FRC doses from 30 U (30 U/10 µg) to 60 U (60 U/20 µg) in steps of 1 unit.

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

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 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 self-administered at any time of the day at the investigator's discretion and at around the same time every day, which remained roughly the same throughout the study. Patients with ongoing insulin glargine treatment from prior to the study, started the run-in at their pre-study dose level. Patients who took insulin detemir before the study started the run-in at a total daily insulin dose of previous insulin minus 20%. For previous basal insulin other than insulin glargine and insulin detemir, insulin glargine at visit 2 was started at the same dose as the previous basal insulin if they were receiving once daily injection or the total daily dose of previous insulin minus 20% if they were receiving more than one daily injection.

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. Therefore, patients switching from insulin glargine to the FRC began treatment at a recommended daily lixisenatide dose of 10 µg, i.e., either 20 U/10 µg given with Peach pen if the dose the day before randomization was <30 U or 30 U/10 µg given with Olive pen if this dose was ≥30 U.

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. The doses were to be titrated once a week based on the insulin glargine dose, until the patient reached a target FSMPG of 80 to 100 mg/dL while avoiding hypoglycemia episodes, according to a standardized algorithm. Thereafter, until the end of the study, the dose was to be adjusted as necessary to maintain FSMPG within target. Dose changes were based on a median of FSMPG values from last 3 days measured by the patient. In both treatment groups a total daily dose >60 U was not allowed. In case a dose >60 U of insulin was required to manage the glycemic levels, the dose was to be capped at 60 U and a rescue medication (fast-acting, insulin glulisine) could be introduced.

Non-investigational medicinal products: Background treatment with metformin and rescue therapy with Insulin glulisine

Formulation: As per approved label

Routes of administration:

Metformin: Oral

Insulin glulisine: Self-administered subcutaneous injection

Dose regimen:

Metformin: Dose regimen was in accordance with locally approved label. If previously taken at a stable dose of at least 1000 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: Short/rapid-acting insulin (insulin glulisine) was introduced as rescue therapy along with the investigational medicinal product (IMP) and metformin at a dose per investigator's discretion, as required to bring under control the patients' glycemic parameters, which were otherwise not controlled with the IMP. The rescue therapy was started as a single daily administration to be given at the main meal of the day (except breakfast in the FRC group).

Duration of treatment: Up to 33 weeks

Duration of observation:

Up to 33 weeks (up to 8-week screening period that includes 2 weeks of screening procedures and 6 weeks of run-in treatment phase + 24-week open-label randomized treatment period + 3-day post-treatment safety follow-up)

Criteria for evaluation:

In this summary, only the safety results are being presented in full. The following safety criteria were evaluated, and analyzed using descriptive statistics:

1. Hypoglycemia as defined below will be assessed
2. Adverse events, serious adverse events, vital signs, ECG, safety laboratory values.

Statistical methods:

Safety analyses

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. Adverse events were summarized by system organ class and preferred term, segregated by whether they were treatment emergent or not. Other safety evaluations such as laboratory evaluations, vital signs, physical examination and electrocardiogram (ECG) were summarized descriptively.

There were no interim analyses performed for the study.

Summary:

Population characteristics

A total of 421 Indian patients from 13 sites, with T2DM (mean duration ~7.5 years) poorly controlled (HbA1c >8%) on basal insulin were screened in the study. Of these patients, 294 patients entered run-in and a total of 248 patients were randomized into either the FRC arm (n=125) or the Insulin glargine arm (n=123). Barring one patient who withdrew post randomization, a total of 247 patients were treated as randomized (safety population), yielding an evaluable per protocol population of 121 patients in each arm (total 242 patient, 1:1 randomization). The demographics and baseline characteristics were well balanced across both treatment groups. The population was predominantly male (about 60%). The median age of the population was 53 years and the mean BMI at screening was 27.35 (4.525) kg/m^2. About 69% of the population had BMI >25 kg/m^2 indicating that most patients were obese. All except 2 patients were on metformin at screening.

Efficacy

Three factors have been identified as having significantly impacted the efficacy outcomes:

- The insufficient titration following noncompliance to protocol algorithm
- Questions regarding the validity of results produced by the central laboratory for primary and key secondary efficacy parameters (HbA1c, FPG and PPG)
- The high number of operational deviations observed in study execution.

Potential errors in sample handling by the central laboratory.

Divergent results were observed between the patient-reported self-measured post prandial glucose values which were consistent with the known expected products profile and the PPG from the central laboratory, showing opposite results. This triggered a Sponsor visit to the laboratory. The visit revealed that the labeling of the vials before analysis was a manual process without appropriate documentation of quality control. These observations posed concerns regarding the validity of the efficacy data.

High number of operational deviations:

About 90% of major protocol deviations were observed in study execution, which hinder the validity of the efficacy results.

Although it is not possible to entirely invalidate the study results, it is also not possible to validate them. Therefore, efficacy results were not presented in this summary.

Safety results

Overall, the FRC was well-tolerated, and there were no new safety signals in any of the safety areas of interest. The safety profile of FRC treatment generally reflected the established safety profiles of its components.

Both arms had good treatment compliance of over 99% each and the same duration of exposure.

Treatment emergent hypoglycemia was reported in 33.9% patients in FRC arm and 37.4% patients in the Insulin glargine arm. No patients experienced severe hypoglycemia. About three quarters of the episodes were asymptomatic (no typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤3.9 mmol/L [70 mg/dL]) with no relevant differences between the treatment arms. Documented symptomatic hypoglycemia events (typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration ≤3.9 mmol/L [70 mg/dL]) were reported by 12 (9.7%) patients in the FRC arm and by 21 (17%) patients in the insulin glargine arm. Documented hypoglycemia (measured plasma glucose concentration <3.0 mmol/L [54 mg/dL]) was reported by 9 (7.3%) patients in the FRC arm and by 10 (8.1%) patients in the insulin glargine arm.

There were no deaths, no SAEs, no cases of overdose, no pregnancy and no AEs that required treatment/ study discontinuation reported in the study.

Treatment emergent AEs were reported in a total of about 32.8% of the safety population (by 33.9% patients in the FRC group and by 31.7% patients in the insulin glargine group). Most of them were of mild intensity, 17% were moderate and 1 event of dyslipidaemia was severe. The TEAEs related to IMP were reported only in the FRC arm (8% patients) and consisted of gastrointestinal disorders such as nausea, vomiting, decreased appetite reflecting the GLP1 RA activity of FRC, and increased lipase. The outcome of over 80% of the events was recovery (either complete or ongoing). There were few treatment differences in the SOCs of events reported. 'Metabolism and nutrition disorders' (12% patients overall) and ‘blood and lymphatic system disorders’ (6.5% patients overall) were the top SOCs, which were both slightly more frequent in Insulin glargine arm. No relevant patterns were observed for the subgroup analyses.

One patient in each arm reported treatment emergent AESIs [increased ALT levels (>3 x ULN)], both asymptomatic.

There were 5 patients with increased lipase >2 ULN (3 patients in FRC, related events in 2 of them; and 2 patients in Insulin glargine arm), 1 patient (FRC) with increased amylase >2 ULN, 2 patients (Insulin glargine arm) with both lipase and amylase elevated >2 ULN and 1 patient (FRC) with increased calcitonin (>20 pg/mL). There were no reports of injection site reactions or allergic/ hypersensitivity reactions.

There were no PCSA in vital signs. Abnormalities in ECG were seen at week 24 in 7.3% patients in FRC and 12.2% patients in the Insulin glargine arm. There were no patients with abnormal findings from vital signs, physical examination or ECG reported as treatment-related TEAEs. Post-baseline clinically significant abnormalities in hematology and clinical chemistry did not show any relevant treatment differences.

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