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Sponsor: Sanofi **Drug substance(s):** Insulin glargine	**Study Identifiers:** U1111-1203-8663, NCT03760991 **Study code:** LPS15396
Title of the study: A multicenter, multinational, prospective, interventional, single-arm, Phase IV study evaluating the clinical efficacy and safety of 26 weeks of treatment with insulin glargine 300 U/mL (Gla-300) in patients with Type 2 diabetes mellitus uncontrolled on basal insulin	
Study center(s): Forty-seven study centers in 14 countries (Argentina, Colombia, Egypt, Hong Kong, India, Indonesia, Lebanon, Malaysia, Peru, Philippines, Saudi Arabia, South Africa, Thailand, and Turkey) consented at least 1 patient.	
Study period: Date first participant enrolled: 16/Jan/2019 Date last participant completed: 05/Oct/2020 Study Status: Completed	
Phase of development: IV	
Objectives: • **Primary objective:** To assess the efficacy of Gla-300 on glycemic control measured by change in hemoglobin A1c (HbA1c) in patients with T2DM uncontrolled with their current basal insulin following the switch to Gla-300 • **Secondary objectives:** To evaluate the effects of Gla-300 on glycemic control To evaluate the safety of Gla-300 To evaluate the effects of Gla-300 on treatment satisfaction To evaluate the effects of Gla-300 on healthcare resource utilization (HCRU) outcomes	
Methodology This was a Phase IV, multicenter, multinational, interventional, single-arm study to evaluate the clinical efficacy and safety of treatment with Gla-300 in patients with T2DM uncontrolled on basal insulin. The study comprised 3 periods: • A screening period of up to 2 weeks • A 26-week treatment period • A post-treatment follow-up phone call visit at Week 27	

The maximum study duration per patient was 29 weeks. Six onsite visits and 5 telephone contacts were scheduled. Additional onsite visits could be scheduled for unexpected investigational medicinal product (IMP) needs. Eligible patients were instructed to perform self-injection of Gla-300 once daily SC.

Impact of the coronavirus disease 2019 (COVID-19) pandemic on study conduct

The COVID-19 pandemic was declared on 11 March 2020 and was ongoing during the conduct of this trial.

Contingency measures were implemented to maintain feasibility, data integrity, and participant safety during the COVID-19 pandemic. These included modifications to trial conduct and administration of trial procedures to allow participants to continue in the trial despite challenging circumstances and modifications to monitoring and/or other trial oversight mechanisms.

Number of participants:

Planned: 430

Enrolled: 493

Treated: 372

Evaluated:

Efficacy:372

Safety: 372

Diagnosis and criteria for inclusion:

Patients with T2DM were enrolled in the study based on the below eligibility criteria.

- Patients >18 years of age (inclusive) at the time of signing the informed consent
- Patients with T2DM on "standard of care" basal insulin therapy, administered once or twice daily as per labeling, for at least 6 months prior to screening visit, with or without oral agents and with or without use of a glucagon-like peptide 1 receptor agonist, approved for using with insulin
- Hemoglobin A1c between 7.5% (58 mmol/mol) and 10% (86 mmol/mol) inclusive, during screening
- A median of the last 3 consecutive fasting self-monitored plasma glucose (SMPG) values prior to baseline, or at least 2 fasting SMPG values in the week prior to baseline >130 mg/dL
- Signed written informed consent

Study products

Investigational medicinal product(s): Insulin glargine 300 U/mL (Gla-300)

Route(s) of administration: subcutaneous (SC), by self-injection

Dose regimen: once daily

Duration of treatment: 26 weeks

Duration of observation: A post-treatment follow-up phone call visit at Week 27

Criteria for evaluation

Primary endpoint:

- Change in HbA1c from baseline to Week 26

Secondary endpoints:

- **Efficacy:**
  - Change in HbA1c from baseline to Week 12
  - Percentage of patients reaching general HbA1c target of <7% at Weeks 12 and 26
  - Percentage of patients reaching targeted fasting SMPG of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) at Weeks 12 and 26
  - Change in fasting plasma glucose (FPG) from baseline to Week 26
  - Change in fasting SMPG from baseline to Week 26
  - Change in 7-point SMPG profile from baseline to Week 26
  - Percentage of patients requiring rescue therapy between Weeks 12 and 26
- **Safety:**
  - Number of patients with at least 1 hypoglycemia from baseline to Week 26
  - Number of patients with adverse events (AEs) and serious adverse events (SAEs) (including hypoglycemic episodes associated with seizures, coma, or unconsciousness)
- **Other endpoints:**
  - Change in treatment satisfaction as measured by insulin treatment satisfaction questionnaire (ITSQ) from baseline to Week 26
  - Number of patients with HCRU (hospitalization, emergency room visits, and office [or specialty] visits) from baseline to Week 26

Statistical methods:

Primary analysis:

The change in HbA1c from baseline to Week 26 was analyzed using a mixed effect linear model for repeated measures with an adequate contrast at Week 26.

This model included fixed categorical effects of visit as well as continuous fixed covariates of baseline HbA1c and baseline HbA1c value-by-visit interaction. This model provided a change from baseline in HbA1c estimate (at Week 12 and Week 26) and the associated standard error and 95% confidence intervals (CI).

The change in HbA1c from baseline to Week 26 was assessed across subgroups of baseline HbA1c category (<8%, ≥8 to <9%, ≥9%). A subgroup analysis was also performed according to the type of prior basal insulin therapy.

A sensitivity analysis, in which data were restricted to the on-treatment period, was performed using the same mixed effect linear model as the primary analysis. A further sensitivity analysis was performed to assess the potential impact of the COVID-19 pandemic on the primary endpoint.

Analysis of secondary endpoints:

The analysis of secondary endpoints was exploratory and descriptive.

The proportion of patients who reached the general HbA1c target of <7% and the fasting SMPG target of 80 to 110 mg/dL at Weeks 12 and 26 were described.

The same model as for the primary analysis was used for the analysis of change from baseline in FPG and fasting SMPG.

A descriptive analysis was performed for the HbA1c change from baseline to Week 12 and the 7-point SMPG profile.

The proportion of patients requiring rescue therapy between Weeks 12 and 26 was described.

Descriptive analyses were performed for the proportion of patients with at least 1 hypoglycemia and for event rates.

Safety analyses on AEs were descriptive.

Change in total treatment satisfaction as measured by the ITSQ from baseline to Week 26 was analyzed using the same model as for primary analysis.

Healthcare resource utilization per country/region and overall was analyzed by descriptive analysis according to glycemic control achievement as assessed by HbA1c (change in value between baseline and Week 26 or based on a given HbA1c target) or according to the occurrence of hypoglycemia.

Multivariate analyses using a logistic regression model were performed to assess the impact of certain covariates on binary endpoints.

Summary Results

Population characteristics:

A total of 493 patients were enrolled in the study. Screening was failed in 121 (24.5%) patients. All 372 eligible patients received study treatment. A total of 11 (3.0%) patients prematurely discontinued study treatment; the most common reasons for treatment discontinuation were AEs, in 5 (45.5%) patients, and withdrawal by subject, in 4 (36.4%) patients. One patient discontinued study treatment during the on-treatment period, due to an AE, but completed the 26-week period.

The mean age of the eligible population was 60.9 (standard deviation [SD]: 10.0) years and there was an equal number of male and female patients (each 186 [50.0%] patients). The mean BMI was 29.57 (SD: 5.43) kg/m2 and most patients had body mass index (BMI) ≥25 kg/m2 (305 [82.0%] patients).

The median (range) duration of diabetes was 12.00 (0.6 to 49.0) years and 246 (66.1%) patients had duration of diabetes ≥10 years. The median (range) duration of last previous basal insulin was 1.40 (0.2 to 28.0) years and the most commonly reported last previous basal insulins were insulin glargine (222 [59.7%] patients; all U100) and insulin neutral protamine Hagedorn (107 [28.8%] patients). A total of 331 (89.0%) patients were treated with previous non-insulin antihyperglycemic agents. The median (range) duration of last previous noninsulin antihyperglycemic treatment was 3.00 (0.0 to 33.0) years and the most commonly reported last previous noninsulin antihyperglycemic treatments were biguanides (304 [81.7%] patients), sulfonylureas (129 [34.7%] patients), dipeptidyl peptidase-4 inhibitors (106 [28.5%] patients), and sodium-glucose co-transporter-2 inhibitors (50 [13.4%] patients). In total, 130 (34.9%) patients had 1 previous noninsulin antihyperglycemic agent, 141 (37.9%) patients had 2 previous noninsulin antihyperglycemic agents, and 60 (16.1%) patients had >2 previous noninsulin antihyperglycemic agents.

Efficacy:

All 372 eligible patients (100.0%) were used for efficacy analyses.

◆ **Primary Efficacy Endpoint**

Regarding the primary objective of the study, Gla-300 demonstrated a robust HbA1c lowering effect in patients with T2DM uncontrolled on previous basal insulin:

- There was clinically significant decrease in mean HbA1c from baseline to Week 12 (-0.66% [95% CI: -0.77%, -0.56%]) and to Week 26 (-0.82% [95% CI: -0.93%, -0.70%])
    - A decrease in least squares mean (LS-mean) HbA1c from baseline to Week 12 and from baseline to Week 26 was seen consistently overall and across all countries and regions with at least 70 evaluable patients (India,

Asia, Latin America, and Middle East Africa); however, at Week 26, the magnitude of the decrease in HbA1c from baseline was numerically smaller for the Middle East Africa region compared with Latin America and India (judged by non-overlapping 95% CI)

- Decreases in LS-mean HbA1c from baseline to Weeks 12 and 26 of a similar magnitude compared with the primary analysis were seen in sensitivity analyses: (1) limited to post-baseline values measured during the on-treatment period only; (2) excluding patients considered as impacted by the COVID-19 pandemic
- Decreases in LS-mean HbA1c from baseline to Weeks 12 and 26 were seen irrespective of baseline HbA1c category (<8%, ≥8% to <9%, ≥9%) or type of prior basal insulin therapy; however, larger decreases were noted in patients with higher HbA1c values at baseline, as expected

◆ **Secondary efficacy endpoints**

Improvements in glycemic parameters were consistently observed with Gla-300 across secondary efficacy measures:

- The percentage of patients who achieved each of the HbA1c targets (<6.5%, 7.0%, <7.5%, and <8.0%) increased from baseline to Week 12 and from Week 12 to Week 26
  - The HbA1c target <7.0% was achieved in 43 (11.6%) patients at Week 12 and 69 (18.5%) patients at Week 26
  - During the 26-week period, the HbA1c target <7.0% was achieved without severe and/or symptomatic documented ≤3.9 mmol/L (70 mg/dL) hypoglycemia event at any time of the day in 61 (16.4%) patients
  - In a multivariate logistic regression model, the HbA1c target <7.0% at Week 26 was less likely to be achieved in patients with baseline HbA1c ≥8% to <9% or ≥9%, compared with <8% (OR: 0.25 [95% CI: 0.13, 0.48] and OR: 0.17 [95% CI: 0.08, 0.34], respectively) and less likely to be achieved in patients enrolled in Middle East Africa compared with other regions, as illustrated by the OR versus Asia (OR: 0.39 [95% CI: 0.18, 0.82])
- There was a decrease in LS-mean FPG from baseline (9.08 [SD: 2.95] mmol/L; 163.63 [SD: 53.17] mg/dL) to Week 12 (-1.44 [95% CI: -1.73, -1.14] mmol/L; -25.86 [95% CI: -31.23, -20.49] mg/dL) and to Week 26 (-1.66 [95% CI: -1.95, -1.37] mmol/L;-29.88 [95% CI: -35.13, -24.63] mg/dL)
- There was a decrease in LS-mean fasting SMPG from baseline (9.00 [SD: 1.82] mmol/L; 162.21 [SD: 32.85] mg/dL) to Week 12 (-1.84 [95% CI: -2.04, -1.65] mmol/L; -33.20 [95% CI: -36.74, -29.66] mg/dL) and to Week 26 (-2.00 [95% CI: -2.19, -1.80] mmol/L); -36.03 [95% CI: -39.54, -32.52] mg/dL)
- The fasting SMPG target of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) was achieved in 127 (34.1%) patients at Week 12 and 136 (36.6%) patients at Week 26
  - In a multivariate logistic regression model, fasting SMPG target of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) at Week 26 was less likely to be achieved in patients enrolled in Middle East Africa compared with other regions, as illustrated by the OR versus Asia (OR: 0.40 [95% CI: 0.22, 0.72])
- Daily profiles showed a decrease from baseline in 7-point SMPG throughout the day at Week 12 and Week 26
- No patients in the eligible population required rescue therapy between Week 12 and Week 26.

◆ **Impact of the COVID-19 Pandemic on Efficacy Results**

- The COVID-19 pandemic was not considered to have had a sizable impact on the efficacy results, as judged by the sensitivity analysis performed on the primary endpoint that excluded patients considered as impacted by the COVID-19 pandemic

Safety results:

All 372 patients (100.0%) in the eligible population received at least 1 dose of study treatment and were included in the safety population.

- **Extent of Exposure**

- The median (range) duration of study treatment was 183.00 (5.0 to 252.0) days
- The mean total daily current basal insulin dose increased from baseline (0.35 [SD: 0.20] U/kg) over the 26-week period, up to 0.50 (SD: 0.24) U/kg at Week 26. Most dose titration occurred within the first 12 weeks of the on-treatment period, with the greatest increase observed within the first 4 weeks

- **Hypoglycemia events**

The overall incidence of hypoglycemia was low; a total of 76 (20.4%) patients who received Gla-300 had at least one treatment-emergent hypoglycemia event in any category:

- Nocturnal hypoglycemia, defined by sleep status, was reported in 35 (9.4%) patients
- Severe hypoglycemia was reported in only 1 (0.3%) patient
- Severe and/or confirmed hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]) was reported in 70 (18.8%) patients
- Symptomatic hypoglycemia was reported in 55 (14.8%) patients (documented plasma glucose ≤3.9 mmol/L [≤70 mg/dL] in 47 [12.6%] patients; documented plasma glucose <3.0 mmol/L [<54 mg/dL] in 14 [3.8%] patients)
- Asymptomatic hypoglycemia was reported in 33 (8.9%) patients

No patients permanently discontinued study treatment due to a hypoglycemia event and no hypoglycemia events

(including severe hypoglycemia) were reported as serious treatment-emergent adverse events (TEAEs).

- **Adverse events**

- Treatment-emergent AEs were reported in a total of 110 (29.6%) patients
- Treatment-emergent AEs were considered by the Investigator to be related to the IMP in 7 (1.9%) patients, to antidiabetic non-IMP in 3 (0.8%) patients, and to pen device in 3 (0.8%) patients
- Treatment-emergent SAEs were reported in a total of 15 (4.0%) patients, including a single TEAE leading to death in 1 (0.3%) patient (Cardiac arrest). No treatment-emergent SAEs were considered related to IMP by the Investigator
- Treatment-emergent AEs leading to IMP discontinuation were reported in a total of 4 (1.1%) patients

- **Impact of the COVID-19 Pandemic on Safety Results**

The COVID-19 pandemic was considered not to have had a significant impact on safety results:

- Treatment-emergent AEs related to COVID-19 infection were reported in 5 (1.3%) patients, including a treatment-emergent SAE related to COVID-19 infection in 1 (0.3%) patient

Other results:

- **Treatment Satisfaction**

Treatment satisfaction increased over time following the initiation of Gla-300 therapy:

- Mean ITSQ total satisfaction score increased from baseline (76.56 [SD: 15.66]) by 7.24 (95% CI: 6.09, 8.39) at Week 12 and by 7.63 (95% CI: 6.39, 8.87) at Week 26. Note: transformed ITSQ total satisfaction scores and domain scores range from 0 to 100, with higher transformed scores indicating better treatment satisfaction.

- Numerical improvements from baseline to Week 12 and to Week 26 were noted for all ITSQ sub-scores (Inconvenience, Lifestyle, Hypoglycemic control, Glycemic control, and Delivery system), especially for the Glycemic control sub-score that increased from baseline (66.00 [SD: 23.81]) by 15.05 (95% CI: 13.25, 16.84) at Week 12 and by 16.05 (95% CI: 14.28, 17.83) at Week 26

◆ **Healthcare Resource Utilization**

Few patients required HCRU from baseline to Week 26:

- Across a total of 183.0 patient-years, no patients required hospitalizations, 3 (0.8%) patients required emergency room visits (3 visits in total [0.02 visits per patient-year]), and 17 (4.6%) patients required out-patient office or specialty visits (29 visits in total [0.16 visits per patient-year])

Post hoc results:

There were consistent decreases in LS-mean HbA1c from baseline to Week 12 and to Week 26, regardless of the change in insulin dose (<0.05 U/kg; ≥0.05 to <0.12 U/kg; ≥0.12 to <0.21 U/kg; ≥0.21 U/kg).

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