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Sponsor: Sanofi	**Study Identifiers:** U1111-1186-2485, NCT03406000
Drug substance(s): INSULIN GLARGINE (U300)	**Study code:** GLARGL08200

Title of the study: A 28-week, prospective, single-arm, phase 4 study to evaluate treatment optimization with once-daily insulin glargine 300 U/mL in combination with prandial rapid-acting insulin analogue in patients with type 1 diabetes previously uncontrolled on twice daily basal insulin as part of basal-bolus therapy

Study center(s): A total of 11 centers screened and randomized at least 1 patient in Brazil

Study period:

Date first subject/patient enrolled: 22/Jan/2018

Date last subject/patient completed: 04/Feb/2019

Phase of development: Phase 4

Objectives: The primary objective of this study was to evaluate the efficacy of switching treatment from twice-daily (BID) basal insulin to once-daily (OD) Insulin glargine HOE901-300 IU/ml as part of basal bolus regime in terms of Hemoglobin A1c (HbA1c) improvement (reduction by at least 0.3%), from baseline to week 24, in uncontrolled type 1 diabetes mellitus patients The secondary objectives were to evaluate other efficacy parameters in terms of glycemic control as well as safety including hypoglycemia events, weight changes, and adverse events (AE) and to evaluate the effect of Insulin glargine HOE901-300 IU/ml on diabetes treatment satisfaction and fear of hypoglycemia as well as patient's satisfaction regarding the number of daily injections

Methodology: This was a 28-week, multicenter, prospective, interventional, single-arm open label phase 4 study.

Number of patients:

Planned: 123

Randomized: Not applicable

Treated: 123

Evaluated:

Efficacy: 123

Safety: 123

Diagnosis and criteria for inclusion: Patients were included in the study if they fulfilled the following criteria: male or female, age ≥ 18 years, with Type 1 diabetes mellitus, being treated BID with any basal insulin in combination with prandial rapid-acting insulin analogue for at least one year; having an HbA1c measurement of 7.5% – 10.0% at study entry, and having signed an Informed Consent Form.

Study treatments

Investigational medicinal product(s): Once-daily insulin glargine HOE901-300 IU/mL (Gla-300; Toujeo®).

Formulation: It was supplied as a sterile, non-pyrogenic, clear, colorless solution in the SoloSTAR® pen (a prefilled i.e.,disposable pen for insulin glargine HOE901-300 IU/mL). Each pen contained in total 450 units of insulin glargine (1.5 mL of 300units/mL insulin glargine solution). This pen allowed dose setting in the range of 1 - 80 units with minimum of 1 unit increment

Route(s) of administration: Subcutaneous

Dose regimen: At the end of the run-in period, Insulin glargine solution HOE901-300 IU/ml was self-administered subcutaneously once daily, preferably in the morning, and at the same time each day as possible. Switching from insulin glargine 100 U to insulin glargine HOE901-300 IU/ml, the recommended starting once-daily dose was the same as the previous daily dose of insulin glargine 100 U (switch on a unit-to-unit basis). Switching from other twice-daily basal insulin products to once-daily insulin glargine HOE901-300 IU/ml, the recommended initial insulin glargine HOE901-300 IU/ml dose was 80% of the total daily dose of basal insulin agent that was discontinued.

Duration of treatment: 24 weeks

Duration of observation: 4-week run-in period, 24-week treatment period and 2-7-day safety follow-up period

Criteria for evaluation:

Efficacy: Mean HbA1c change from baseline to Week 24

Mean HbA1c change from baseline to Week 12; Mean change in fasting plasma glucose (FPG) from baseline to Week 12 and Week 24; Mean change in fasting self-monitored blood glucose (SMBG) from baseline, Week 8, Week 12 and Week 24; Mean change in 8-point SMBG from baseline to Week 12 and Week 24; Proportion of patients achieving HbA1c target of <7.0% at Week 12 and Week 24; Proportion of patients achieving HbA1c target of <7.0% at Week 12 and Week 24 without hypoglycemia during the last 4 weeks of treatment; Mean change in body weight from baseline to Week 12 and Week 24; Mean change in daily insulin doses (basal, prandial, total) from baseline to Week 24; Proportion of patients achieving HbA1c improvement from baseline to week 24 of at least 0.3% without nocturnal hypoglycemia (documented <70 mg/dl) and/or severe hypoglycemia (between 00.00 and 05:59 am SMBG) during the last 4 weeks of treatment; Proportion of patients with any improvement in HbA1c from baseline to week 24 and decrease in occurrence of nocturnal hypoglycemia (nocturnal defined as time between 00.00 and 05:59 am) evaluated during the 4-week run-in period and the last 4 weeks on-treatment period; Proportion of patients with no deterioration in HbA1c from baseline to week 24 and decrease in occurrence of nocturnal hypoglycemia (nocturnal defined as time between 00.00 and 05:59 am) evaluated during the 4-week run-in period and the last 4 weeks on-treatment period; Proportion of patients with no deterioration in HbA1c from baseline to week 24 and no increase in occurrence of nocturnal hypoglycemia evaluated during the 4-week run-in period and the last 4 weeks on-treatment period

Safety: Number and proportion of patients experiencing hypoglycemia and number of hypoglycemic events per patient-year during the run-in period, the first 8 weeks of Gla-300 treatment period, during the whole Gla-300 treatment period, and during the last 4 weeks of the study. Hypoglycemic events will be recorded according to definitions (sympthomatic, confirmed ≤70mg/dL and <54mg/dL, and/or severe, confirmed ≤70mg/dL and <54mg/dL) and according to the time (nocturnal defined as time between 00.00 and 05:59 am, and at any time of the day); Frequency of AEs/serious AEs (SAEs).

Patient reported outcomes: Change in diabetes treatment satisfaction questionnaire status version (DTSQs) from screening to baseline, from baseline to Week 12 and 24, and from Week 12 to Week 24; Mean change from screening to baseline, baseline to Week 12 and Week 24, and Week 12 to Week 24 on the DTSQ total treatment satisfaction, hyperglycemia perception, and hypoglycemia perception scales; Mean change from baseline to Week 24 on the Adult Low Blood Sugar Survey (Hypoglycemia Fear Scale; HFS-II) Behavior, Worry, and Total scores; Patient's satisfaction with the number of injections per day, and importance for the patient of decreasing the number of basal insulin injections assessed on a 7 point Likert scale (6=very satisfied; 0=very dissatisfied)

Statistical methods: The primary efficacy population is the Intent-To-Treat (ITT) population, which includes all patients eligible for the Insulin glargine HOE901-300 IU/ml treatment phase. The safety population was defined as all patients who did actually received at least one dose of Investigational Medicinal Product (IMP), regardless of the amount of treatment administered. Baseline value was the last available value obtained prior to the first dose of IMP.

The primary efficacy endpoint, change in HbA1c from baseline to Week 24, was analyzed using a mixed linear model for repeated measures carried out via PROC MIXED (SAS) using an adequate contrast at Week 24. it was also provided 95% confidence intervals (CIs) and p-value.

The change from baseline to Week 12 in HbA1c, and change from baseline to Week 12 and Week 24 in FPG as well as in fasting SMBG to Week 8, Week12 and Week24 were analyzed using the same approach as the one used for the primary efficacy endpoint. Mean 8-point SMBG profile at baseline, Week 12 and Week 24, and mean change from baseline to Week 12 and Week 24 for each SMBG time point was described. The proportion of patients reached HbA1c target (<7.0%) at Week 12 and Week 24 (with/and without hypoglycemia in the last 4 weeks of treatment preceding the given visit), as well as incidence of patients with improvement (or no deterioration) in HbA1c with decrease (or no increase) in occurrence of nocturnal hypoglycemia (comparing 4-week run-in period and last 4 weeks on-treatment period) were determined along, with corresponding 95% Clopper-Pearson CI.

Observed change from baseline and relative change from baseline daily insulin doses (basal, prandial, total), defined by the average daily insulin doses made by using daily doses computed on a weekly basis, were described by visit. In case of any missed doses, corresponding days were not taken into account in the determination of the average daily insulin doses.

The percentage of patients experiencing hypoglycemia, as well as the number and rate of hypoglycemia experienced during the run-in period, prior to Insulin glargine HOE901-300 IU/ml first administration, was used as baseline assessment. The proportion of patients with at least 1 hypoglycemia event and the number and rate of hypoglycemia events were determined per hypoglycemia category, for each study period of interest, according to time of occurrence (nocturnal i.e., from 00:00 to 05:59 am, any time of the day).

Change from baseline to Week 12 and Week 24 in body weight was analyzed using the same approach as the one used to analyze the primary endpoint.

The mean change from screening to baseline, baseline to Week 12 and Week 24, and Week 12 to Week 24 on the DTSQs total treatment satisfaction, hyperglycemia perception, and hypoglycemia perception scales was calculated. The total treatment satisfaction was analyzed using the same method as for the primary efficacy endpoint. Hyperglycemia and hypoglycemia perceptions scales being discrete and ordinal, non-parametric tests were preferred to parametric ones. Time points were compared using the Friedman's test followed when significant by two-by-two Wilcoxon's tests. The mean change from baseline to Week 24 on the HFS-II scale: Behaviour, Worry, and Total scores were analyzed using the same method as for the primary efficacy endpoint. The patient 'satisfaction with the number of injections per day and importance for the patient of decreasing the number of basal insulin injections assessed on a 7-point Likert scale (6=very satisfied; 0=very dissatisfied) were analyzed using a Wilcoxon's paired test.

No formal interim analysis was performed during the study.

Summary:

Population characteristics: Overal165 patients were screened and 40 were screen failures. The run-in period was performed by 125 patients, however two of them were considered screen failures of the run-in as they completed the run-in when the target number of patients had been reached. Therefore, 123 patients constituted the ITT population and the safety population. Ten patients did not meet all the inclusion/exclusion criteria at V1 (baseline), but as the information was only made available after visit was performed and patient treatment started, these patients were kept in the ITT. From the 123 patients, eight were prematurely discontinued from IMP and 6 were treated for less than 165 days. The Completed population consisted of 109 patients.

At screening (V0), in the ITT population (N=123), patients (67 [54.5%] females and 56 [45.5%] males) were 37.0 ± 11.5 years-old (mean ± SD) with a median of 35 years, and minimum and maximum of 18 years and 65 years, respectively. The disease duration was 17.0 ± 9.5 years. The patients had a BMI of 26.3 ± 4.1 kg/m². The mean value (± SD) of HbA1c and FPG at screening (Visit V0) were, respectively, 8.6 ± 0.7% and 201 ± 80.3mg/dL. Four patients (3.3%) were smokers. Forty-seven patients (38.2%) consumed alcohol daily, weekly or monthly and 75 (61.0%) patients reported that had never taken alcohol during the last twelve months. A total of 442 concomitant medication were taken by 108 (87,8%) patients of the ITT population. Before study treatment initiated, most of the patients were using glargine as basal insulin: 77 (63%) patients at Visit V0 and 82 (67%) patients at Visit V1. The mean dose of basal insulin was 19.6 (SD=10.4) UI at A.M. and 14.0 (SD=7.1) at P.M. It was observed an increase in the mean total basal insulin dose from Week 0 to Week 24 of 4.72 (SD=9.93) UI and an increase of 0.06 (SD=0.11) UI/Kg between both visits. In terms of relative change, it was observed an increase of 18.31 (SD=64.35) % UI and an increase of 17.12 (SD=32.25) % UI/Kg in basal insulin doses, from Week 0 to Week 24.Lispro was the prandial insulin used for the majority of patients in both visits V0 and V1: 60 (49%) and 50 (41%), respectively. The total dose of prandial insulin was 0.34IU/kg (SD0.16) at V1 and 0.34 (SD0.18) IU/kg at V4. It was observed an increase in the mean total insulin dose from Week 0 to Week 24 of 4.35 (SD=13.85) UI and an increase of 0.05 (SD=0.19) UI/Kg between both visits. In terms of relative change, it was observed an increase of 9.31 (SD=25.98) % UI and an increase of 7.97 (SD=24.54) % UI/Kg in total insulin doses, from Week 0 to Week 24. The ratio between basal and prandial insulin doses was 0.58 (SD=0.13) at Week 0 and 0.61 (SD=0.13) at Week 24, with a change of 0.04 (SD=0.11) between weeks

Efficacy results: The primary efficacy endpoint, change in HbA1c from baseline to week 24 in the ITT population was not achieved in the study. The primary analysis through the least squares means difference (LSM) using a Mixed-effect Model with Repeated Measures (MMRM) approach was estimate = 0.0134, p-value=0.8736, 95%CI [-0.1526 : 0.1793]. The estimate was calculated using the HbA1c values at Week 24 minus the value at baseline. Using the same approach, two sensitivity analysis were performed, with the same result of non-statistically significance between baseline and week 24:

- 24-week on-treatment: comprising ITT population using in the model only HbA1c values performed until 7 days after last dose of HOE901-300 IU/mL (LSM estimate=0.0239, p-value=0.7755, 95%CI [-0.1416 : 0.1894]).
- Completed population: patients from ITT population who completed the 24-on treatment, i.e. at least 165 days (LSM estimate=-0.0239, p-value=0.7774, 95%CI [-0.1909 : 0.1431]

Regarding the secondary efficacy endpoint, change in Hb1Ac from baseline to week 12, using the same models there was also no statistically difference: LSM estimate=-0.1198, p-value=0.1397, 95%CI [-0.2793 : 0.0397]. The estimate was calculated using the HbA1c values at Week 12 minus the value at baseline. For the change in FPG, from baseline to week 24, the analysis of results through LSM also did not reveal statistical difference: Week 12: LSM estimate=-3.2652, p-value=0.7310, 95%CI [-22.0206 : 15.4903]. Week 24: LSM estimate=-11.7185, p-value=0.2576, 95%CI [-32.1122 : 8.6753]. The estimate was calculated using the FPG values at Weeks 12 and 24 minus the value at baseline. The change in SMBG from baseline at Week 8, Week 12 and Week 24 in the ITT population showed a significant statistical decrease. The estimate was calculated using the SMBG values at Weeks 8, 12 and 24 minus the value at baseline:

- Week 8: LSM estimate= -10.2294; p-value=0.0109; 95%CI [-18.0608 : -2.3981].
- Week 12: LSM estimate= -17.7819; p-value<0.0001; 95%CI [-25.9027 : -9.6611].
- Week 24: LSM estimate= -18.7766; p-value<0.0001; 95%CI [-26.6677 : -10.8855].

Change in 8-point SMBG was also measured at weeks 12 and 24, revealing a statistically significant decrease between SMBG baseline and weeks 12 and 24 at pre-breakfast, post-breakfast and post-dinner and from baseline to Week 24 for the pre-dinner timepoint.

Safety results: In the Safety population, the mean duration of exposure to the IMP was 23.7 ± 3.3 weeks, with a median of 24.1 weeks and a minimum and maximum of 2.14 weeks and 29.71 weeks, respectively. There were 135 AEs in 60 out of 123 patients (52.9%) of the Safety population, during the whole study period: 15 during the pretreatment period in 13 [10.6%] patients, 118 during the treatment period [TEAEs] in 55 [44.7%] patients and 2 during the post-treatment period in 2 [1.6%] patients. Among the TEAEs, 11 AEs in 7 out of the 123 patients (5.7%) were considered severe and consisted of Abdominal pain (1 case), Headache (1 case), Hypoglycemia (3 cases), Hypoglycemia seizure (1 case), influenza (1 case), Musculoskeletal pain (1 case), nasopharynghitis (1 case), neck pain (1 case) and sinusitis bacterial (1 case). Among the TEAEs, 5 AEs in 5 out of the 123 patients (4.1%) were considered related to the IMP and consisted of hypoglycemia (4 cases) and hypoglycemia seizure (1 case). Six SAEs were reported during the treatment period by 6 out of 123 patients (4.9%). They consisted of Fetal death (1 case), Hypoglycemia (2 cases), Hypoglycemic seizure (1 case), Syncope (1 case) and Urinary tract infection (1 case). Three of them, reported by 3 out of 123 patients (2.4%) were considered related to the IMP: Hypoglycemia (2 cases), Hypoglycemia seizure (1 case). One AESIs occurred in one patient and consisted of Pregnancy. One Symptomatic overdose with IMP was reported, consisted of Convulsive crisis secondary to severe hypoglycemia episode. There were 3 (2,4%) pen related events reported, not related to adverse events.

A total of 2920 hypoglycemic events were reported by 117 patients (95.1%) in the Safety population. The proportion of patients experiencing any hypoglycemia event during the 4-week run-in period and during the last 4-weeks on treatment period were compared using the McNemar's test. It was found a statistically significant decrease from run-in to the last 4-weeks on treatment period in the proportion of patients with at least one hypoglycemic event (p=0.0253).

In terms of basal insulin dose there was a statistically significant increase in the mean total basal insulin doses from V1 to V4 (LSM estimate = 4.649, p-value<0.001, 95%CI [2,9537;6.3444]. In term of percentage it was an increase of 18.31% IU.

Patient reported outcomes: The results of the DTSQS total satisfaction with treatment revealed a statistically significant difference between week 12 and baseline as well as week 24 and baseline (p-value <0.0001 in both cases). There was an increase in the total satisfaction, in both cases. A Friedman's test comparing the three time points Week 0 (baseline), Week 12 and Week 24 for the item Perceived Hyperglycemia revealed a statistically significant difference (p-value<0.0001) between all three visits. The same test was applied for the item Perceived Hypoglicemia, comparing the same timepoint, and no significant statistical difference was revealed (p-value=0.1280). A paired t-test revealed statistically significant improvement of the scores from baseline to Week 24 for HFS-II Behaviour (p=0.0361), HFS-II Worry (p-value=0,0094) and HFS-II Total (p-value=0.0051). For the comparison of patient´s satisfaction score (satisfaction with the number of injections) at baseline (V1) and Week 24 (V4), a Wilcoxon's paired test comparing both time points was performed, showing a statistically significant improvement in the level of satisfaction (N=122, S=1834.4, p-value<0.0001). On the other hand, there was no statistical difference when comparing the importance of the reduction in the number of basal insulin injections between baseline and Week 24.

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