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Sponsor/Company: Sanofi **Drug substance:** insulin glargine	**Study Identifiers:** NCT01461577, UTN U1111-1118-8753 **Study code:** LANTU_L_05477
Title of the study: A multicenter, open-label, single-arm, 24-week phase IV study evaluating the effectiveness and safety of treatment of insulin glargine in type 2 diabetes mellitus following glucagon-like peptide-1 (GLP-1) failure	
Study centers: 13 centers in Japan	
Study period: Date first patient enrolled: 07/Nov/2011 Date last patient completed: 25/Dec/2012	
Phase of development: Phase 4	
Objectives: Primary objective: To assess the efficacy of insulin glargine as measured by the change in HbA_{1c} (glycosylated hemoglobin) levels from baseline in type 2 diabetes mellitus (T2DM) patients following GLP-1 failure. Secondary objectives: To determine the change in glycemic control, safety, and treatment satisfaction in insulin glargine use in patients following GLP-1 failure. • Changes of HbA_{1c} levels at weeks 12 and 24 from baseline • Responder rate (HbA_{1c} levels <7%) without severe hypoglycemia at weeks 12 and 24, and in case of early termination (ET) • Responder rate (HbA_{1c} levels <6.5% and <7%) at weeks 12 and 24, and ET • Changes of Fasting Plasma Glucose (FPG) and Postprandial Plasma Glucose (PPG) levels from baseline to weeks 4, 6, 12, 16, and 24, and ET • Changes of beta-cell marker: C-peptide from baseline to week 24 and ET • Changes of lipid profile: Lipid profile from baseline to week 24 and ET • Weight change from baseline to weeks 12 and 24, and ET • Insulin dose • Health status & patients' treatment satisfaction: Diabetes Treatment Satisfaction Questionnaire (DTSQs) screening, weeks 6 and 24, and ET; EuroQOL five dimensions questionnaire (EQ-5D) screening, week 24 and ET; and Diabetes Treatment Satisfaction Questionnaire change version (DTSQc), week 24 and ET.	
Methodology: Multicenter, open-label, single-arm, 24-week study	
Number of patients: Planned: 100 Treated: 89 **Evaluated:** Efficacy/pharmacodynamics: 85 Safety: 89	

Diagnosis and criteria for inclusion:

Patients with T2DM, aged ≥30 and ≤75 years, under continuous treatment with stable doses of GLP-1 analogue for >3 months (for patients also using oral antidiabetics [OADs], continuous treatment with stable doses of OADs for >3 months prior to Visit 1), and with HbA_{1c} levels measured at Visit 1 ≥7.5%.

Study treatments

Investigational medicinal product: Lantus® SoloSTAR®/Insulin glargine

Formulation: 100 Units/mL solution for injection in a prefilled SoloSTAR pen (3 mL)

Route of administration: Subcutaneous injection in the abdomen

Dose regimen:

Patients were started on insulin glargine at an initial dose of 4 units a day from Visit 2. Insulin glargine was administered once a day in the morning. Patients visited without injecting the GLP-1 analogue at Visit 2. Titration of insulin dose was performed referred with the median FPG value for the last 3 consecutive days according to the titration algorithm.

Patients were dispensed a blood glucose meter and a patient diary at Visit 1. Patients were instructed on the use of blood glucose meters at this time and asked to start practicing after Visit 1. Physicians provided instruction for the correct use of the blood glucose meter and Lantus SoloSTAR pen at Visit 2.

The general rule was that the FPG value used for this titration is the median of the last three values. If the FPG value was below 70 mg/dL, then the titration was done using the FPG value.

Patients were empowered to adjust their insulin doses under the investigator's supervision. If needed, patients contacted the investigator by phone when adjusting their dose.

Titration scheme: Patients used the median of their last 3 consecutive FPG values to perform the titration. They titrated their insulin dose every 3 days.

Patients were to follow the titration regimen as provided in the table below.

Small departure from the titration scheme was allowed (eg, decrease of the insulin glargine dose), based on investigator's judgment and patient's situation.

Fasting Plasma Glucose (mg/dL)	Insulin Dose
FPG ≤56	Dose decrease (2 U or more) at physician's discretion and upon physician's clinical judgment
≤70 or symptomatic hypoglycemia*	-2 U
70< FPG and ≤110	No change
110< FPG and ≤160	+2 U
FPG >160	+4 U

* Occurring independently of the FPG and defined as symptoms of hypoglycemia responding to ingestion of carbohydrate or an episode associated with a blood glucose level ≤56 mg/dL [≤3.1 mmol/L].

Duration of treatment: 24 weeks

Duration of observation: 26 to 27 weeks (including the period from screening through the end of the study)

Criteria for evaluation:

Efficacy/pharmacodynamics:

- Changes of HbA_{1c} levels at weeks 12 and 24 from baseline

- Responder rate (HbA_{1c} levels <7%) without severe hypoglycemia at weeks 12 and 24, and in case of ET

- Responder rate (HbA_{1c} levels <6.5% and <7%) at weeks 12 and 24, and ET

- Changes of FPG and PPG levels from baseline to weeks 2, 6, 12, 16, and 24, and ET

- Changes of beta-cell marker: C-peptide from baseline to week 24 and ET

- Changes of Lipid profile: Lipid profile from baseline to week 24 and ET

- Weight change from baseline to weeks 12 and 24, and ET

- Insulin dose

- Health status & patients' treatment satisfaction: DTSQs– screening, weeks 6 and 24, and ET; EQ-5D–screening, week 24 and ET; and DTSQc–week 24 and ET

Safety:

Adverse events (AEs) reported by the patient or noted by the investigator, clinical laboratory data (total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol), vital signs (body weight, blood pressure, and heart rate), and hypoglycemia (symptomatic, nocturnal, and severe).

Statistical methods:

Efficacy analyses were based on the modified Intent To Treat (mITT) population consisting of all treated patients, who had at least 1 day exposure to insulin glargine. Safety analyses were based on the safety population which included all patients exposed to investigational product.

The analyses of the primary efficacy and key secondary efficacy variables were also performed using the per-protocol population, defined as a subset of the mITT population containing patients without a major efficacy-related protocol deviation.

Determination of sample size:

Primary endpoint was the change of HbA_{1c} levels from baseline to week 24/EOT.

Based on the assumption of an expected HbA_{1c} change of 0.7% at week 24 assuming a standard deviation of 2.0, and based on an expected baseline HbA_{1c} of 8.5% (inclusion range is 7 to 10%), 100 patients were needed considering a 15% of non evaluable patients.

Analysis was done using a paired t-test; a 2-sided 95% confidence interval (CI) of the difference in HbA_{1c} change (baseline-end of study) with a power of 90% was calculated.

Statistical methods (continued):

Efficacy analysis:

- Analysis of primary efficacy endpoint
  - HbA_{1c}: Primary endpoint was the change of HbA_{1c} levels from baseline to week 24. Analysis was done by a one sample t-test; point estimate and 2-sided 95% (CI) of the difference in HbA_{1c} change were calculated.
- Key secondary efficacy endpoints
  - HbA_{1c}: Changes from baseline to weeks 12 and 24 visit values within time allowance were analyzed using a paired t-test. The consecutive changes were plotted in figures. Responder rates (HbA_{1c} levels <6.5% and <7%) were tabulated by baseline categories using the mITT population.
  - FPG: Changes from baseline to each post-baseline visit (observed cases) and end of treatment (EOT) (final visit using last observation carried forward [LOCF]) were analyzed using a paired t-test. The consecutive changes for FPG were plotted in figures. Changes from baseline to Visit 14/EOT for average 7-point plasma glucose were summarized by descriptive statistics. The consecutive changes for 7-point plasma glucose were plotted in figures.
  - Quality of life: DTSQs, DTSQc, and EQ-5D were summarized by descriptive statistics and cross tables of change from baseline. Each score and subscore was done by a one sample t-test and was represented by histogram. Then, total score of EQ-5D was calculated using the Japanese version.

Safety analysis:

- Adverse event: AE data were summarized by treatment group using frequency tables. Vital signs focused on descriptive statistics.
- Hypoglycemia: Hypoglycemia was categorized by “Symptomatic hypoglycemia”, “Nocturnal hypoglycemia”, and “Severe hypoglycemia”. The number of patients with symptomatic hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia was summarized by descriptive statistics. The number of episodes of symptomatic hypoglycemia and nocturnal hypoglycemia was plotted using histogram by an onset time of 4 weeks. Moreover, the number of patients with symptomatic hypoglycemia and severe hypoglycemia was plotted using histogram by onset time by onset hour.

Summary:

Population characteristics:

A total of 89 Japanese adults with T2DM (47 male and 38 female subjects in mITT population), 35 to 75 years of age (median: 64.0 years) with body mass index (BMI) ranging from 15.5 to 27.7 kg/m^2 (median: 24.03 kg/m^2) were included in the study.

Efficacy/pharmacodynamic results:

The primary objective of the study was to assess the efficacy of insulin glargine as measured by the change in HbA_{1c} levels from baseline in T2DM patients following GLP-1 failure.

Based on the primary analysis, insulin glargine demonstrated statistically significant reduction of HbA_{1C} from baseline to endpoint (mean difference =-0.86%; p-value <0.0001).

There was no patients for each target HbA_{1c} value (<6.5% and <7.0%) at baseline, 3 patients and 14 patients reached each target value (<6.5% and <7.0%, respectively) at LOCF.

Regarding the secondary endpoints, insulin glargine demonstrated statistically significant reduction of C-peptide levels from baseline to Week 24 and LOCF (mean difference = -0.94; p-value = <0.0001 at LOCF), but not for lipid parameters (total cholesterol, triglyceride, HDL-C, and LDL-C). Insulin glargine demonstrated statistically significant increase of body weight from baseline to Week 12 (mean difference = +2.66 kg; p-value = <0.0001), Week 24 (mean difference = +3.82 kg; p-value = <0.0001) and at LOCF (mean difference = +3.76 kg; p-value = <0.0001).

Moreover, insulin glargine was considered to contribute to the improvement of quality of life of patients following GLP-1 failure, and patients reported a significant improvement in DTSQ treatment satisfaction score.

All sub-scores of DTSQs showed statistically significant difference in change from baseline:

- Treatment Satisfaction score increased from 23.6 at baseline to 25.3 at LOCF, showing a significant difference between baseline and endpoint (p =0.0149).
- Hyperglycemic score decreased from 3.7 at baseline to 2.9 at LOCF, showing a significant difference between baseline and endpoint (p =0.0003).
- Hypoglycemic score increased from 0.8 at baseline to 1.7 at LOCF showing a significant difference between baseline and endpoint (p <0.0001).

Safety results:

The incidence of all treatment emergent adverse events (TEAEs) was 85.4% (76/89). Hypoglycemia (60 patients, 67.4%), Nasopharyngitis (12 patients, 13.5%), Upper respiratory tract infection, headache and back pain (4 patients, 4.5%) were the most frequently reported preferred terms.

The incidence of TEAEs that led to permanent treatment discontinuation was 5.6% (5/89).

Serious TEAEs were reported in 3 patients (3.4%). All serious TEAEs were considered as not related to the investigational medical product (IMP). No patients experienced serious hypoglycemia.

A total of 57 patients (64.0%) experienced 446 symptomatic hypoglycemia events. The number of events per patient years was 11.4. Thirty-eight episodes of nocturnal hypoglycemia (per protocol definition) were reported in 17 patients (19.1%), with a number of events per patient years of 1.0.

After 17 weeks, the number of symptomatic hypoglycemia and nocturnal hypoglycemia decreased.

No nocturnal hypoglycemia episodes were reported in the last 4 weeks. No severe symptomatic hypoglycemia and no hypoglycemic event that led to treatment discontinuation were reported.

Sixty patients (67.4%) experienced TEAEs considered possibly related to IMP: hypoglycemia in 60 patients (67.4%), edema peripheral in 2 patients (2.2%), headache in 1 patient (1.1%), dizziness in 1 patient (1.1%), eyelid edema in 1 patient (1.1%), vision blurred in 1 patient (1.1%), pruritus generalized in 1 patient (1.1%), and pollakiuria in 1 patient (1.1%).

A significant increase in body weight was observed with insulin glargine ($p<0.0001$).

Insulin glargine was considered as safe and well tolerated in Japanese patients with T2DM.

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