These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** HOE901 (insulin glargine)	**Study Identifiers:** UTN U1111-1116-2926, NCT01234597 **Study code:** LANTU_L_05146
Title of the study: A comparative study evaluating the effect of prandial treatment adjustment, based on continuous blood glucose monitoring, on glucose control in type 2 diabetes patients who are not controlled by treatment with once daily basal insulin	
Study center(s): The study was conducted across 11 sites in Israel	
Study period: Date first patient enrolled: 26/Dec/2012 Date last patient completed: 13/Apr/2015	
Phase of development: Phase 4	
Objectives: To evaluate the effect of prandial treatment adjustment, based on continuous blood glucose monitoring, on glucose control in type 2 diabetes patients who are treated with once daily basal insulin or mixed insulin, and require treatment with basal plus regimen.	
Methodology: This was a 24 week, randomized, open-label, controlled, multicenter, phase IV pilot study conducted at 11 sites across Israel between December 2012 and April 2015. The study was conducted to evaluate the effect of prandial treatment adjustment, based on continuous blood glucose monitoring, on glucose control in type 2 diabetes mellitus (T2DM) patients who were not controlled by treatment with once daily basal insulin or mixed insulin. T2DM patients aged >21 years with glycated hemoglobin (HbA_{1c}) ≥8% continuously treated with basal insulin or mixed insulin once daily for 6 months, and not using short-acting insulin or mixed insulin more than once daily for 3 weeks during the last 6 months were included in the study.	
Number of patients**:**	Planned number of patients to be included in run-in period: 200 Patients enrolled to the run-in period: 219 Planned number of patients to be randomized: 70 to 100 Patients Randomized: 121
Evaluated:	Efficacy: 121 Safety: 121
Diagnosis and criteria for inclusion: Type 2 diabetes patients with HbA_{1c} ≥8% continuously treated with basal insulin or mixed insulin once daily for the last 6 months were included in run-in period.	

Study treatments

Investigational medicinal product(s): Lantus® (Insulin glargine) 100 u/mL. Injection solution in a ready-to-use SoloSTAR® pen (3 mL) for subcutaneous (SC) use.

Formulation: Injection solution

Route(s) of administration: Subcutaneous

Dose regimen: At baseline visit, the initial dose, similar to that with which the patient entered the study, was adjusted. All patients started taking basal insulin in the evening. After determining the initial insulin glargine dose and initiating treatment, fasting blood glucose (FBG) was measured daily by the patient using a glucometer. Every three days, the patient titrated the dose according to the mean FBG of the last three days according to the following scheme:

FBG value	Insulin glargine Dose change
FBG ≥100 mg/dl	Increase by 2 units
100 > FBG ≥70 mg/dl	No dose change
FBG <70 mg/dl	Decrease by 2 units

This titration was continued until Week 8. From Week 8 onwards, the dose of insulin glargine remained unchanged throughout the study.

Apidra® (Insulin glulisine) 100 u/mL. Injection solution in a ready-to-use SoloSTAR® pen (3 mL) for SC use.

Formulation: Injection solution

Route(s) of administration: Subcutaneous

Dose regimen:

Arm A: SC administration of insulin glulisine 0-15 minutes before the first meal of the day. The initial dose was 6 units. The titration upwards was determined by the Investigator in order to reach the target value of 2h-pp blood glucose (BG) <135 mg/dL).

Arm B: Insulin glulisine SC administration 0-15 minutes before the meal with the highest elevation in the glucose level. The initial dose was based on 6 units and increased according to preprandial glucose SF/(100-). Where SF= 2*insulin glargine dose/1700. The titration upwards was determined by the investigator in order to reach the target value of 2h-pp BG <135 mg/dL.

Duration of treatment: 16 weeks

Duration of observation: 8 weeks of run-in + 16 weeks of intensified treatment

Non-investigational medicinal product(s): Oral metformin and Dipeptidyl Peptidase-4 (DPP-4) treatment dose was adjusted as per Investigator's decision at the first visit, and kept constant throughout the study, except for hypoglycemia events and/or other adverse events.

Criteria for evaluation:

Efficacy:

Primary endpoint: This was a pilot study assuming a difference of 0.5% in mean HbA_{1c} values in favor of the group of patients using a sensor, as compared to the group of patients without a sensor.

Secondary endpoints: Comparison between the two study arms in terms of:

1. Rate of hypoglycemia events.
2. Insulin glargine and glulisine dose.

Safety: Adverse events reported by the patient/subject or noted by the Investigator.

Statistical methods:

Descriptive statistics:

All measured variables and derived parameters were listed individually and tabulated by descriptive statistics.

For categorical variables summary tables were provided giving sample size, absolute and relative frequency by study group.

For continuous variables summary tables were provided giving sample size, arithmetic mean, standard deviation, median, minimum, maximum and 95% CI (Confidence Interval) for means by study group.

Baseline characteristics and safety analysis:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).

The Chi square test was applied for testing the statistical significance of the difference in frequency of adverse events between the study groups.

T-test was applied for analyzing the difference between the 2 study groups or between the two insulin type groups in all relevant continuous baseline characteristics.

Chi-square test was applied for analyzing the difference between the 2 study groups or between the two insulin type groups in all relevant continuous baseline characteristics.

Efficacy analysis:

The two samples T-test was applied for analyzing the differences in the following parameters between the study groups:

- Glycated hemoglobin level at Week 24 and the change from Week 8 to Week 24;
- Fasting plasma glucose (FPG) level at Week 24 and the change from Week 8 to Week 24;
- Glulisine and glargine doses at Week 24.

T-tests and chi-square tests were applied for analyzing the differences in the following parameters between the study groups:

- 7-points of glucose values at visit 3 and 5 and the change from Week 12 to Week 24.

Chi square test was applied for testing the statistical significance of the difference in frequency of patients who experienced any hypoglycemic event during the study between the study groups.

Logistic regression was applied for analyzing the above difference with adjustment to gender, age, duration of diabetes, insulin dose, FPG and HbA_{1c} levels at Visit 3 and another time also adjusted by insulin type groups.

Non-parametric Wilcoxon test was applied for testing the statistical significance of the difference in number of hypoglycemic events per patient between the study groups.

Summary:

Efficacy results: Change in HbA_{1c} was observed in both study groups, after the addition of prandial insulin treatment (Week 8 to Week 24). The HbA_{1c} level significantly decreased in both groups. ($p<0.01$) but there was no significant differences between the study groups ($p=0.75$). Mean HbA_{1c} decreased in 0.48% for arm A and in 0.54% for arm B.

The mean daily dose of insulin glargine at Week 24 was 40.4 ± 18.4 (±SD) for arm A and 36.3 ±16.9 (±SD) for arm B. No statistically significant difference between insulin glargine doses at Week 8 between the study arms.

The mean daily dose of insulin glulisine at Week 24 was 9.3± 4.5 (±SD) for arm A and 10.1±4.6 (±SD) for arm B. No statistically significant difference between insulin glulisine doses at Week 24 was observed in the two study groups.

No significant difference was found in the mean glucose values at all the 7 time points at Week 24.

The FPG level significantly increased from Week 8 to Week 24 in both groups. (p=0.02 for arm A and p<0.01 for arm B). The mean change between FPG level from Week 8 to Week 24 for arm A and arm B was 19.37 ±55.10 (95% CI: 3, 35.73) and 27.41 ±60.93 (95% CI: 9.10, 45.72), respectively. There were no significant differences between the two study groups (p=0.51). Safety results: In this study, no statistically difference between arm A and B in frequency of hypoglycemia events, no deaths, and no severe hypoglycemic events were reported. There were no new safety signals.
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