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Sponsor / Company: Sanofi **Drug substance(s):** insulin glargine (HOE901)	**Study Identifiers:** NCT01658579, U1111-1130-3593 **Study code:** PDY12777
Title of the study: A 16-week, randomized, open-label, controlled study comparing the efficacy and safety of a new formulation of insulin glargine versus Lantus in patients with type 1 diabetes mellitus	
Study center(s): 3 centers in US	
Study period: Date first patient enrolled: 13/Jul/2013 Date last patient completed: 28/Apr/2013 (last patient completed treatment); 24/May/2013 (last patient last visit)	
Phase of development: 2	

Objectives:

Primary objective:

To compare the glucose during treatment with a new formulation of insulin glargine (HOE901-U300) and Lantus in adult patients with type 1 diabetes mellitus (T1DM).

Secondary objectives:

To compare HOE901-U300 and Lantus given in the morning or in the evening regarding continuous glucose monitoring (CGM) data:

- diurnal glucose exposure;
- diurnal glucose stability as measured by rate of change in median curve;
- diurnal glucose variability as measured by interquartile range (IQR);
- mean and variation in glucose profiles;

To compare HOE901-U300 and Lantus regarding (HbA_{1c}), self-measured plasma glucose (SMPG) (fasting plasma glucose, prior to injection of study drug, 7 point profiles);

To compare the incidence and frequency of hypoglycemic episodes, both symptomatic, confirmed by plasma glucose ≤70 mg/dL (American Diabetes Association [ADA] criteria) and CGM-detected;

To assess the safety and tolerability of HOE901-U300.

Methodology: Multicenter, open-label, randomized, 4-arm parallel-group, comparative Phase 2 study comparing HOE901-U300 and Lantus in patients with T1DM who have been on a basal plus mealtime insulin regimen for at least one year. Patients were randomized to receive once daily basal insulin (HOE901-U300 or Lantus) and to the sequence of the injection time during study period A and study period B (morning then evening or evening then morning) with a ratio of 1:1:1:1. No formal sample size estimation was performed for this exploratory study.

Number of patients**:**	Planned: 56
	Randomized: 59
	Treated: 59
Evaluated:	
	Efficacy: 59
	Safety: 59

Diagnosis and criteria for inclusion: Male or female patients, between 18 and 70 years of age, inclusive, with T1DM for at least one year on a basal plus mealtime insulin regimen and glycated hemoglobin A_{1c} (HbA_{1c}) ≤9% having signed the written informed consent form were eligible for the study. Key exclusion criteria: patients receiving >0.5 U/kg body weight basal insulin and patients not on stable insulin dose (± 20% total basal insulin dose) in the last 30 days prior to screening visit; hospitalization for diabetic ketoacidosis or history of severe hypoglycemia (requiring 3rd party assistance) in the last 6 months prior to randomization

Study treatments

Investigational medicinal product(s): Tested drug - HOE901-U300; Control drug - HOE901-U100 (Lantus)

Formulation: HOE901-U300: solution for injection containing 300 U/mL insulin glargine (new formulation)

Lantus® (U100): solution for injection containing 100 U/mL insulin glargine (marketed product)

Route(s) of administration: Subcutaneous (SC) injection once daily in the morning or evening.

The tested drug HOE901-U300 was supplied as 300 U/mL insulin glargine solution for SC injection in 3 mL cartridges and the control drug.Lantus was supplied as insulin glargine solution for SC injection 100 U/mL in 10 mL vials, both to be used with commercially available insulin syringes:

• for HOE901-U300 (all doses) and for Lantus doses of 1–30 U insulin glargine: BD Ultra-Fine™ Short Needle Insulin Syringe with half-unit-scale [8 mm (5/16") x 31 G];

• for Lantus doses >30 U insulin glargine: BD Ultra-Fine™ Short Needle Insulin Syringe [8 mm (5/16") x 31 G] with whole unit scale.

Dose regimen: Dosing of insulin glargine given as HOE901-U300 or Lantus was done based on self-measured, fasting, pre-breakfast plasma glucose levels (target range 80–130 mg/dL; 4.4–7.2 mmol/L), and taking into account also the presence of hypoglycemia. Minimum dose increments for the basal insulin were to be 1.5 U.

Once daily injection in the morning or evening for 8 weeks during Period A then in the evening or morning respectively for another 8 weeks during Period B according to randomization.

Starting dose:

- Patients on Lantus, NPH or insulin detemir once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to the daily basal insulin doses on the day prior to the baseline visit.
- Patients on NPH or insulin detemir more than once daily prior to the baseline visit: 80% of total daily NPH or insulin detemir dose (= total daily dose reduced by 20%) on the day prior to the baseline visit.

Noninvestigational medicinal product(s): Patients in all treatment groups continued with their fast-acting mealtime insulin analogue (ie, insulin glulisine, insulin lispro or insulin aspart) during the study.

Formulation: Solution for SC injection

Route of administration: SC injection

Dose regimen: Dosing of the mealtime insulin was done based on self-measured, pre-prandial and postprandial plasma glucose levels and the carbohydrate content of the meal. The target range for 2-hour postprandial plasma glucose was <160 mg/dL (8.9 mmol/L). Mealtime insulin doses could be reduced as basal insulin doses were increased. Dose recommendations for the mealtime insulin were provided in the study protocol.

Duration of treatment: 16 weeks

Duration of observation:

The study consisted of:

- Up to 4-week screening and training period including 2-week CGM;
- 2x8-week comparative efficacy and safety treatment period with CGM blinded to the patients;
- After study completion or permanent discontinuation of study treatment: 4-week post-treatment safety follow-up period.

In total the maximum study duration was up to 24 weeks per patient**.** CGM blinded to patients was continuously used starting from screening visit 2 (week -2) until visit end-of-treatment visit 18 (week 16).

Criteria for evaluation:

Efficacy:

Primary endpoint: Percent (%) of time in glucose range of 80-140 mg/dL (4.4-7.8 mmol/L) during week 7 and 8 within treatment period A and during week 15 and 16 in treatment period B based on CGM.

CGM-based secondary endpoints are:

- Percent time above the upper limit of glycemic range (%time in hyperglycemia);
- Percent time below the lower limit of glycemic range (%time in hypoglycemia);
- Diurnal glucose exposure;
- Diurnal glucose stability as measured by rate of change in median curve;
- Diurnal glucose variability as measured by IQR;
- Mean and variation in glucose profiles;
- Average time within glycemic range (≥80 mg/dL and ≤140 mg/dL) in the last four hours of each dosing interval during 14 days of CGM usage in the last 2 weeks of the 8 weeks treatment period;
- Area below the CGM profile and above the upper limit of the glycemic range (140 mg/dL) (hyperglycemic AUC normalized (divided by total time period);
- Area above the CGM profile and below the lower limit of the glycemic range (80 mg/dL) (hypoglycemic AUC normalized [divided by total time period]).

Safety/Tolerability:

<u>Hypoglycemia:</u>

Hypoglycemia was analyzed by hypoglycemia categories as defined by ADA, by their diurnal distribution (0:00-24:00), by time of the day (nocturnal starting between 00:00 and 05.59 hours; daytime starting between 06:00 and 23:59) and by sleep status (occurring after going to bed in the evening and before getting up in the morning [before administration of any insulin] when patient was asleep and woke up due to hypoglycemia).

- Incidence (%) patients with at least one hypoglycemia per category and event-rate per patient year of exposure
- CGM-detected hypoglycemic episodes.

<u>Other safety and tolerability analyses:</u>

Other safety and tolerability analyses included evaluation of injection site reactions, hypersensitivity reactions, adverse events (AEs), serious adverse events, physical examination, vital signs, laboratory data, electrocardiogram (ECG).

Statistical methods:

The primary endpoint was analyzed using a linear mixed model with treatment (HOE901-U300 or Lantus) and period (treatment period A or B) as fixed effects, and patient as random effect. Adjusted mean estimates for each treatment with standard errors, the adjusted estimate of treatment mean difference with standard error and a 95% confidence interval for the treatment mean difference were provided. The statistical test was two-sided tests at a nominal 5% significance level. The same model was used for secondary efficacy endpoints %time in hyperglycemia/hypoglycemia, diurnal glucose exposure, diurnal glucose stability and diurnal glucose variability. Other efficacy endpoints were descriptive. CGM related parameters were analyzed based on the CGM population, non-CGM parameters were based on the modified intent-to-treat (mITT) population.

Safety analyses were descriptive, based on the safety population.

Summary: The current report presents the final efficacy and safety results.

Overall, 59 patients were randomized in 3 centers in USA to 1 of 4 treatment groups (15 patients in the HOE901-U300 morning then evening injection group, 15 patients in the HOE901-U300 evening then morning injection group, 15 patients in the Lantus morning then evening injection group, and 14 patients in the Lantus evening then morning injection group). All patients were treated with the investigational medicinal product (IMP) and included in the analyses. Four patients (6.8%) prematurely discontinued study treatment, 1 due to AE (pregnancy) in the HOE901-U300 group, and 3 in the Lantus group due to other reasons. With the cross-over design the patients had to switch from morning to evening injections and vice versa. Therefore overall, 30 patients received HOE901-U300 in the morning, 29 patients received HOE901-U300 in the evening, 28 patients received Lantus in the morning, and 28 patients received Lantus in the evening. The relatively small sample size per group (n=14 to 15) should be considered for the interpretation of the results. The safety and mITT populations were identical to the randomized population.

The demographic and patient characteristics at baseline were generally similar across the 4 treatment groups. All patients were Caucasian. The mean age of the randomized population was 44.2 years; 57 of 59 (96.6%) patients were younger than 65 years. 54.2% of the patients were male. Gender was evenly distributed between HOE901-U300 and Lantus although there appeared to be some asymmetry in the distribution of gender between the 4 treatment groups due to the small sample size. At baseline, 27.1% of patients had a BMI ≥30 kg/m2. Disease characteristics, including diabetic history and diabetes complications, were generally comparable among the 4 treatment groups. As prior antidiabetic medications, all randomized patients had used insulins and analogs, of which 88.1% had received insulin glargine, and 3.4% used additional biguanides prior to the study. During the last 14 days prior to randomization, the mean total (basal and mealtime) insulin daily dose was 49.33 U (0.603 U/kg). For the overall study population, mean values for HbA_{1c} at baseline were generally comparable across the 4 treatment groups in the randomized population.

Efficacy results:

Primary endpoint: During the last 2 weeks of each 8 week treatment period, the time spent within glycemic range (4.4-7.8 mmol/L [80–140 mg/dL]), as measured by CGM, was comparable in the HOE901-U300 group and the Lantus group (LS mean HOE901-U300: 31.75%; Lantus 30.99%, LS mean difference 0.75% [95% CI: -3.614 to 5.124]). In the last 4 hours at Weeks 7 and 8 and Weeks 15 and 16 respectively, these percentages slightly increased for the combined HOE901-U300 group (Week 7 and 8: 32.08%; Weeks 15 and 16: 33.02%) and decreased for the combined Lantus group (Weeks 7 and 8: 29.07%; Weeks 15 and 16: 28.7%), which is in agreement with the duration of action of HOE901-U300 beyond 24 hours.

Notably, the upper limit (7.8 mmol/L [140 mg/dL]) of the glycemic range defined for the primary efficacy endpoint was ambitious, as it is lower than the titration target for the prandial insulin (<8.9 mmol/L [<160 mg/dL] 2 hours postprandial) in this study and lower than the target set by the ADA for peak postprandial capillary glucose <180 mg/dL.

A slightly larger increase of time in glycemic range from baseline was observed in the combined HOE901-U300 group (mean change: Weeks 7 and 8: 4.628%; Weeks 15 and 16: 4.221%) than in the combined Lantus group (mean change: Weeks 7 and 8: 1.637%; Weeks 15 and 16: 0.455%).

Secondary endpoints: During the last 2 weeks of each 8-week treatment period, percent time above the upper limit of glycemic range of 7.8 mmol/L (140 mg/dL) was comparable between treatment groups (58.24% in the HOE901-U300 group and 57.38% in the Lantus group in LS mean), so was the percent of time below the lower limit of 4.4 mmol/L (80 mg/dL) with 10.01% in the HOE901-U300 group and 11.64% in the Lantus group in LS mean.

The diurnal glucose exposure, stability, and variability at Weeks 7 and 8 in Period A and at Weeks 15 and 16 in Period B) were similar in all treatment groups.

During the 16 weeks of study treatment, for HbA_{1c}, FPG, pre-injection SMPG and mean average 7 point profiles, similar results were observed in both combined groups.

At baseline, the total insulin daily dose was higher in the HOE901-U300 group than in the Lantus group (53.54 U [0.68 U/kg] versus 50.08 U [0.59 U/kg]) and continued to be higher until Week 8 (55.79 U [0.67 U/kg] versus 51.45 U [0.59 U/kg]). However, the difference between them diminished at Week 16 (57.40 U [0.67 U/kg] versus 54.80 U [0.63 U/kg]), because of an increase of the total daily insulin dose in the Lantus group, whereas the dose remained stable in the HOE901-U300 group.

With regards to the ratio of basal/total insulin dose, an increase of the basal insulin portion in the total daily insulin dose from baseline to Week 16 was observed similarly in the HOE901-U300 group (baseline: 0.47; Week 16: 0.53) and in the Lantus group (ration of basal to total insulin, baseline: 0.53; Week 16: 0.52).

During the 4 week post treatment period, commercial basal insulin doses and total insulin doses were slightly and similarly reduced (by up to -4.00 U [-0.05 U/kg] in the former HOE901-U300 group and by -1.45 U [-0.02 U/kg] in the former Lantus group).

Overall, the efficacy of HOE901-U300 in patients with T1DM was comparable with that of Lantus, with an overall trend to better glycemic control than with Lantus:

- Comparable time spent in glycemic target range at Weeks 7 and 8 and Weeks 15 and 16 as measured by CGM;
- Trend of larger mean increase of time spent within glycemic target range from baseline at Weeks 7 and 8 and Weeks 15 and 16 as measured by CGM
- Trend towards more time spent within glycemic target range in the last 4 hours prior to basal insulin injection at Weeks 7 and 8 and Weeks 15 and 16 as measured by CGM;
- Comparable time spent below the lower limit of glycemic range (4.4 mmol/L [80 mg/dL]) during the last 2 weeks of each treatment period, even though there was a trend of slightly larger mean increase from baseline in time spent in hypoglycemic range with HOE901-U300 as measured by CGM;
- Comparable diurnal glucose stability and diurnal glucose variability at Weeks 7 and 8 and Weeks 15 and 16 as measured by CGM;
- Trend of larger mean decrease of time spent in high hyperglycemic (>180 and >250 mg/dL) ranges as measured by CGM;
- With regards to average glucose as measured by CGM by hour of the day over the entire 16 week period, flatter profile observed with HOE901-U300 than with Lantus (peaks and troughs observed with HOE901-U300 are consistently within a narrower range than those observed with Lantus).

HOE901-U300 and Lantus morning and evening injections were separately analyzed. Given in the evening, both, HOE901-U300 and Lantus were comparable with regards to time spent in glycemic range, number and distribution of measurements outside of glycemic range, average glucose variation. For morning injections, there was a trend in favor of HOE901-U300 compared to Lantus morning injections, because a larger increase of time spent in glycemic target from baseline to the last 2 weeks of both treatment periods could be seen. With HOE901-U300 morning injections, also a smaller number of measurements below glycemic target could be seen compared to Lantus morning injections, while this number was comparable with evening injections. The number of measurements above glycemic target was not influenced by either morning or evening injections of both, HOE901-U300 and Lantus. With regards to average glucose by hour of the day, the flattest profile was achieved with HOE901-U300 morning injections. These results suggest that HOE901-U300 could be administered once daily either in the morning or in the evening to achieve good glycemic control.

Safety results:

Hypoglycemia:

Overall, hypoglycemic events, regardless of the category, time of day, and study period, were reported by a slightly lower or similar percentage of patients in the HOE901-U300 group than in the Lantus group. Differences in favor of HOE901-U300 were even more evident for nocturnal hypoglycemia (occurring between midnight and 05:59 hours). The lower incidences of patients with nocturnal hypoglycemia were not at the expense of higher incidences of daytime hypoglycemia, which also occurred at similar or lower percentages, although differences were mostly small.

The possible tendency for lower percentages of hypoglycemia events with HOE901-U300 compared to Lantus that was more apparent with evening injection of IMP should be interpreted with caution due to the low number of patients. However, the percentage of patients with at least one hypoglycemia was:

- similar in the morning and evening injection groups within the HOE901-U300 group;
- similar in the HOE901-U300 morning injection groups and the Lantus morning injection groups;
- lower in the HOE901-U300 evening injection groups than in the Lantus evening injection groups;
- higher in the evening than in the morning injection groups within the Lantus groups

The lower or comparable incidences of hypoglycemia any time of the day and particularly the lower incidences for nocturnal hypoglycemia events in the HOE901-U300 group could already be seen during the first 6 weeks of treatment, when basal insulin was titrated after changing over from the pre-study basal insulin or after the cross-over from IMP morning injections to IMP evening injections or vice versa. The favorable results for HOE901-U300 were maintained during the last 2 weeks (maintenance phase) of both periods.

Analyses of hypoglycemia event rate per patient year exposure yielded results in favor of HOE901-U300 as well. Overall, the hypoglycemic events per patient year were similar (asymptomatic hypoglycemia) or lower (all other categories) in the HOE901-U300 group than compared with the Lantus group (any categories of events, HOE901-U300: 127.40; Lantus: 144.51). This was especially true for severe and/or confirmed hypoglycemia ≤3.9 mmol/L (70 mg/dL) and even more for those <3.0 mmol/L (<54 mg/dL) during any time of the day, whose event rate adjusted by exposure was lower in the HOE901-U300 group during any hour of the day.

The number of patients with severe hypoglycemia was low in both IMP groups and none were serious or led to treatment discontinuation.

Hypoglycemia detected by CGM (maximally around 288 interstitial glucose measurements a day) provided an approximately threefold higher number of events in both groups than compared with hypoglycemia as measured by sporadic SMPG and recorded into the eCRF. The profile by hour of day derived from the SMPG data recorded in the eCRF was slightly different, but confirmed in both groups a lower rate of nocturnal hypoglycemic events and an increase of the event rate in the afternoon. Overall, CGM could detect a shorter total duration of hypoglycemic events (≤3.9 mmol/L [70 mg/dL] and <3.0 mmol/L [<54 mg/dL]) for the HOE901-U300 group, compared with the Lantus group.

Within the HOE901-U300 and Lantus group, consistent with the comparable numbers of hypoglycemia events as measured by CGM for morning and evening injections, a comparable rate of hypoglycemia per patient year of exposure as measured by SMPG and recorded into the eCRF for morning and evening injections was found.

The favorable numerical trends in the HOE901-U300 group should be interpreted with caution because of the small number of patients.

During the 4-week post-treatment period, after the switch to commercial basal insulin, the number of patients reporting hypoglycemia events of any category was comparable in both groups, suggesting no issues with the switch back from HOE901-U300 to commercially available U100 basal insulin.

Adverse Events:

The percentage of patients with any treatment-emergent AEs (TEAEs) was higher in the HOE901-U300 group (24/30 [80.0%]) than in the Lantus group (19/29 [65.5%]). In the HOE901-U300 group, one patient experienced serious intestinal obstruction (unrelated to IMP) and another patient discontinued treatment due to pregnancy. No death was reported during the study. The only TEAEs (mild insomnia, moderate rash, and mild injection site pain) considered related to IMP treatment were reported in 3 patients, 10.0% in the HOE901-U300 group.

There were no events of major adverse cardiovascular events, increased alanine aminotranferase, malignant neoplasm or overdose.

TEAEs potentially linked to injection site reactions were observed in 2/30 [6.7%] patients of the HOE901-U300 group, and in 1/29 [3.4%] patient of the Lantus group. One event in each group was considered related to mealtime insulin rather than IMP. There was no concern regarding TEAEs potentially linked to hypersensitivity reaction which occurred in 4/30 (13.3%) patients of the HOE901-U300 group and in 1/29 (3.4%) patient of the Lantus group. Of these events, only 1 event (moderate rash [bilateral rash on top of feet]) in the HOE901-U300 group was considered related to IMP. This event resolved after 38 days while HOE901-U300 was continued.

Other Safety:

Overall, there were no particular safety issues or signals identified in reviewing the clinical laboratory data for liver parameters, and other laboratory data. No potentially clinically significant abnormality in clinical laboratory parameters was reported as a TEAE.

Overall, there were no particular safety issues or signals identified in reviewing the data for blood pressure, heart rate, weight, and ECG status.

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