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Sponsor / Company: Sanofi **Drug substance(s):** Insulin glargine (HOE901)	**Study Identifiers:** NCT01676233, U1111-1129-3633 **Study code:** PDY12335
Title of the study: A randomized, open-label, 2-treatment crossover study of a new formulation of insulin glargine comparing to Lantus® on 24-hour glucose profile in Japanese patients with type 1 diabetes mellitus on treatment with basal-bolus insulin	
Study center(s): 1 center in Japan	
Study period: Date first patient enrolled: 12/Sep/2012 Date last patient completed: 08/Aug/2013	
Phase of development: Phase 1	
Objectives: **Primary:** To compare the 24-hour glycemic profile in continuous glucose monitoring (CGM) between a new formulation of insulin glargine (HOE901-U300) and Lantus at steady state **Secondary:** • To compare the change of fasting plasma glucose (FPG), self monitoring of plasma glucose (SMPG), and postprandial plasma glucose (PPG) between the 2 treatments • To compare the efficacy of the 2 treatments on glycemic control in glycemic parameters (1,5-anhydroglucitol [1,5 AG], glycoalbumin, and hemoglobin A_{1c} [HbA_{1c}]) • To compare the occurrence of hypoglycemia between the 2 treatments • To assess the safety and tolerability of HOE901-U300	
Methodology: Single-center, randomized, open-label, active control, repeated dose, crossover (2-sequence, 2-period, and 2-treatment with no washout period between treatment periods) study.	
Number of patients**:** Planned: 20 Randomized: 20 Treated: 20 **Evaluated:** Efficacy: 20 Safety: 20 Pharmacokinetics: 20	
Diagnosis and criteria for inclusion: Japanese patients aged over 20 years with type 1 diabetes mellitus (T1DM) on treatment with basal-bolus insulin.	

Study treatments

Investigational medicinal products: HOE901-U300 (Test) and Lantus (Comparative)

Formulation:

HOE901-U300: Solution containing insulin glargine (300 U/mL)

Lantus: Solution containing insulin glargine (100 U/mL)

Route of administration: Subcutaneous (SC) injection

Dose regimen: The dose of HOE901-U300 or Lantus was individually up-titrated. If previous basal insulin was administered twice daily (BID) or once daily (QD) in the morning, the basal insulin regimen was changed to QD at bedtime at Visit 1 (screening). If Lantus was administered BID, the previous total daily dose was given QD. If previous basal insulin other than Lantus was administered BID, then 80% of the previous total daily dose was given QD.

HOE901-U300

The starting dose of HOE901-U300 (Treatment Period 1 or Treatment Period 2) was at a dose divisible by 1.5 and did not exceed the previous QD basal insulin dose. After administration of the starting dose, the dose of HOE901-U300 was adjusted individually to achieve a target glycemic goal of 80 to 130 mg/dL in FPG measured by SMPG according to the titration schedule.

Lantus

The starting dose of Lantus (Treatment Period 1 or Treatment Period 2) was the same as the previous QD basal insulin dose. After administration of the starting dose, the dose of Lantus was adjusted individually to achieve the target glycemic goal of 80 to 130 mg/dL in FPG measured by SMPG according to the titration schedule. The timing of administration of HOE901-U300 and Lantus was at the same time throughout the entire study period (bedtime), and it was preferable to administer HOE901-U300 or Lantus at 3 hours or more after administration of the evening meal bolus insulin.

Noninvestigational medicinal product: Marketed mealtime insulin such as insulin lispro, aspart, and glulisine

Route of administration: SC injection

Duration of treatment: 57 days

Duration of observation: Approximately 66 days including screening (7 days [+7 days, -3 days]), Treatment Period 1 (28 days ± 3 days), Treatment Period 2 (29 days ± 3 days), and Follow-up (2 days ± 1 day).

Criteria for Evaluation:

Efficacy:

Primary: Absolute area under the concentration time curve (AUC) above and below the individual average plasma glucose value (AGV) on the 2nd day of CGM (AUC_{mean_24h}).

(Note): 1st day: 0-24 hours data from 3 days of CGM (Day -3 to Day -2, Day 26 to Day 27, and Day 54 to Day 55)
2nd day: 24-48 hours data from 3 days of CGM (Day -2 to Day -1, Day 27 to Day 28, and Day 55 to Day 56)
3rd day: 48-72 hours data from 3 days of CGM (Day -1 to Day 1, Day 28 to Day 29, and Day 56 to Day 57)
(1st day and 2nd day were conducted in hospital)

Secondary:

- Absolute AUC above and below the individual AGV on the 2nd day of CGM at nocturnal time (AUC_{mean_noc}) and at daytime ($AUC_{mean\_daytime}$)
  - Nocturnal time, 0:00 to 06:00; Daytime, 06:00 to 24:00.
- Absolute AUC above and below the defined blood glucose value (80, 100, 120, and 140 mg/dL) on the 2nd day of CGM (AUC_{value_24h}), at nocturnal time (AUC_{value_noc}), and at daytime ($AUC_{value\_daytime}$)
- J-Index (Parameter to measure current glycemic variability)
- M value (Parameter to measure deviation from the ideal blood glucose)
- Hyperglycemic index, hypoglycemic index and Index of Glycemic Control (ICG)
- Mean Amplitude of Glycemic Excursions (MAGE)
- Mean of Daily Difference (MODD)
- Parameters from target blood glucose (TBG) range (80 to 140 mg/dL)
  - Duration of TBG range over 24 hours ($Dur_{\_TBG[80-140]}$)
  - Rate of TBG range over 24 hours ($Rate_{\_TBG[80-140]}$)
  - AUC above (140 mg/dL) and below (80 mg/dL) plasma glucose value on the 2nd day of CGM ($AUC_{\_over140}$, $AUC_{\_under80}$, respectively)
- Range [min-max] of glucose value during 3 hours just before bedtime injection ($BG_{\_Just\ before\ inj}$)
- Maximum duration within fixed blood glucose value range ($Dur_{\_within30mg/dL}$, $Dur_{\_within60mg/dL}$, $Dur_{\_within90mg/dL}$, and $Dur_{\_within120mg/dL}$).
  - Duration of fixed blood glucose range (30 , 60, 90, and 120 mg)
  - Duration of fixed blood glucose range (30, 60, 90, and 120 mg) in nocturnal term
- Minimum blood glucose range of fixed hour (16, 18, 20, and 22 hours) residence time
  - (MIR_16hRT, MIR_18hRT, MIR_20hRT, MIR_22hRT, and MIR_24hRT)
- Change in FPG, SMPG, and PPG from overall baseline to each treatment end, by treatment
- Change in glycemic parameters (1,5 AG, glycoalbumin, and HbA_{1c}) from overall baseline to each treatment end, by treatment
- Change in daily insulin dose from overall baseline to each treatment end, by treatment (absolute and per kg body weight):
  - Change in daily basal insulin dose
  - Change in daily mealtime insulin dose
  - Change in daily total insulin dose

Safety: Patients were monitored for safety via adverse events (AEs) spontaneously reported by the patients or observed by the Investigator, injection site and hypersensitivity reactions, clinical laboratory data, vital signs, electrocardiogram (ECG), hypoglycemia, and immunogenicity (presence of anti-insulin antibodies).

Pharmacokinetics: The concentration observed just before treatment administration during repeated dosing (C_{trough}) of insulin glargine at steady state for both treatments was measured.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Blood samples for the analysis of serum insulin glargine were collected at Day -3 or Day -2 (baseline), Day 26 or Day 27, and Day 54 or Day 55. Blood samples were taken just before the injection of bedtime insulin (marketed basal insulin or Investigational Medicinal Products [IMPs]).

Concentrations of serum insulin glargine were analyzed using a radioimmunoassay nonspecific for insulin with a lower limit quantification of 5.02 µU/mL.

Statistical methods:

Efficacy: The difference in variability between HOE901-U300 and Lantus on 24-hour CGM was examined by exploratory analysis using AUC_{mean_24h}. Using glucose data from only the 2nd day of CGM, the log transformed AUC_{mean_24h} ratio between the 2 formulations with 90% confidence intervals (CIs) was analyzed with a linear mixed effect model with fixed terms for sequence, period, and formulation, and with an unstructured 2 by 2 matrix of formulation-specific variances and covariances for subject within sequence blocks.

For nocturnal analysis, the variability in blood glucose was evaluated using the same analysis approach as for 24-hour CGM.

The changes in FPG, SMPG, PPG, 1,5 AG, glycoalbumin, and HbA_{1c} from overall baseline to each treatment end were analyzed.

Safety: The evaluation of IMP and active comparator was based on the review of individual numbers and values of hypoglycemic events, anti-insulin antibodies, major adverse cardiac events (MACE), AEs, vital signs, ECGs, hematology and biochemistry (out of normal range and potentially clinically significant abnormalities [PCSAs]), and descriptive statistics. Treatment-emergent adverse events (TEAEs) were tabulated (counts and percents) by formulation. End-of-study PCSAs in clinical laboratory test results, vital signs, and ECGs were listed.

Pharmacokinetics: Descriptive statistics for C_{trough} for each period were provided by treatment and C_{trough} values were listed by treatment, patient, and period.

Summary:

Population characteristics:

A total of 20 patients with T1DM were randomized to 1 of 2 treatment sequences: Lantus in Treatment Period 1 followed by HOE901-U300 in Treatment Period 2 (n=10), HOE901-U300 in Treatment Period 1 followed by Lantus in Treatment Period 2 (n=10). All 20 patients completed the study.

Demographic and baseline characteristics were balanced between treatment sequences except for mean daily insulin doses. The patients that received HOE901-U300 first (n=10) had higher mean basal and mealtime insulin doses at baseline than the patients who received Lantus in the first treatment period (n=10). The mean age of the study population was 52.1 years. All patients were Asian/Oriental. The mean body mass index at baseline was 23.36 kg/m². The mean HbA_{1c} at baseline was 8.21% and the mean FPG at baseline was 7.79 mmol/L (140.3 mg/dL).

Efficacy results:

Primary efficacy endpoint:

The mean (standard deviation [SD]) AUC_{mean_24h} (2nd day of CGM) value was slightly lower for HOE901-U300 compared to Lantus (59756.55 [24577.90] min*mg/dL and 60409.12 [19925.75] min*mg/dL), respectively. The point estimate of the treatment ratio was 0.959 (90% CI: 0.794 to 1.158).

Graphical presentation of mean CGM profiles from Day 2 18:00 to Day 3 24:00 of CGM periods (Figure 1) suggested similar glucose variability over time between the HOE901-U300 and the Lantus treatments

Secondary efficacy endpoints:

The AUC_{mean_noc} value (0:00 to 06:00 of the 2nd day of CGM) for HOE901-U300 was slightly lower compared to Lantus. Mean (SD) of AUC_{mean_noc} was 5337.21 (3467.41) min*mg/dL for HOE901-U300 and 5551.80 (4304.49) min*mg/dL for Lantus. The point estimate of the treatment ratio was 0.939 (90% CI: 0.693 to 1.273).

The duration of TBG over 24 hours was comparable for each treatment. The mean (SD) of $Dur_{\_TBG(80-140)}$ was 8.71 (5.92) hours for the HOE901-U300 group and 8.63 (5.18) hours for the Lantus group. Point estimate of treatment ratio was 0.958 (90% CI: 0.330 to 2.781).

To eliminate the influences of glycemic excursions by meals and snacks, MIR_16hRT, MIR_18hRT, MIR_20hRT, MIR_22hRT and MIR_24hRT were evaluated and were comparable between the 2 treatments. The means (SD) of MIR_16hRT, MIR_18hRT, MIR_20hRT, MIR_22hRT, and MIR_24hRT were 81.21 (31.83) mg/dL, 103.42 (39.61) mg/dL, 127.63 (49.21) mg/dL, 157.37 (57.86) mg/dL, and 200.79 (62.65) mg/dL in the HOE901-U300 group and 84.65 (33.82) mg/dL, 105.60 (39.13) mg/dL, 129.00 (45.09) mg/dL, 152.25 (49.05) mg/dL, and 198.20 (59.31) mg/dL in the Lantus group respectively.

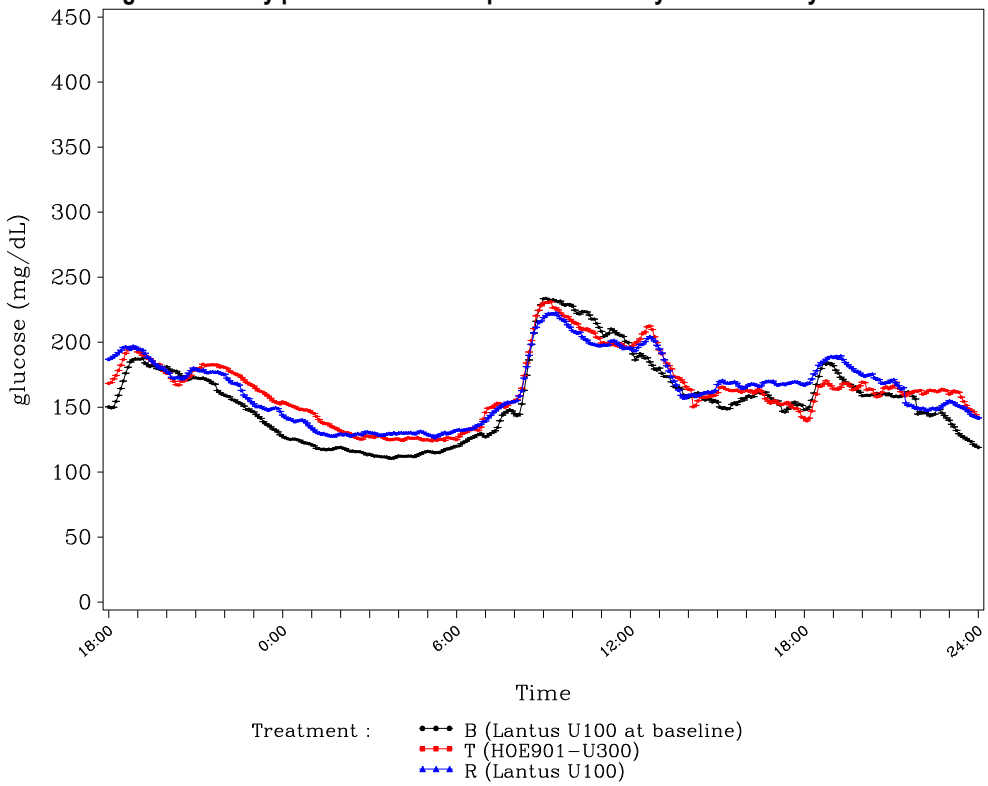
Glycemic control appeared to be comparable between the 2 treatments with similar mean changes from baseline observed in 1,5 AG, glycoalbumin, and HbA_{1c}.

For 1,5 AG, the changes from baseline ranged from -1.16 to 4.26 µmol/L (-0.19 to 0.70 µg/mL) for patients given Lantus followed by HOE901-U300 and from 3.35 to 6.15 µmol/L (0.55 to 1.01 µg/mL) for patients given HOE901 U300 followed by Lantus.

For glycoalbumin, the changes from baseline ranged from -1.15% to 0.28% for patients given Lantus followed by HOE901-U300 and from -1.31% to -0.39% for patients given HOE901-U300 followed by Lantus.

For HbA_{1c}, the changes from baseline in each period were -0.27% and -0.13% for patients given Lantus followed by HOE901-U300 and were -0.28% and -0.25% for patients given HOE901-U300 followed by Lantus.

Figure 1-Overlay plots of mean CGM profiles from Day 2 18:00 to Day 3 24:00



CGM=continuous glucose monitoring
This figure is plotted using mean value by 5 min.

Basal insulin doses generally increased from the overall baseline for both treatment sequences (at baseline of Period 1/overall baseline, the mean daily basal insulin dose was 14.85 units in the HOE901-U300 group and 11.70 units in the Lantus group; at endpoint of Period 1, HOE901-U300: 18.13 units; Lantus: 13.14 units; at baseline of Period 2, HOE901-U300: 12.75 units; Lantus: 18.40 units; at endpoint of Period 2, HOE901-U300: 14.53 units; Lantus: 18.10 units).

Mean mealtime insulin daily doses were generally stable within both sequence arms throughout the study (at baseline of Period 1, HOE901-U300: 30.60 units; Lantus: 24.90 units; at endpoint of Period 1, HOE901-U300: 29.90 units; Lantus: 24.50 units; at baseline of Period 2, HOE901-U300: 25.40 units; Lantus: 29.80 units; at endpoint of Period 2, HOE901-U300: 25.24 units; Lantus: 29.59 units).

Mean basal and mealtime insulin doses (total insulin) at baseline for patients given HOE901-U300 in Period 1 followed by Lantus in Period 2 were higher than those of patients given Lantus in Period 1 followed by HOE901-U300 in Period 2.

Safety results:

There were no treatment-emergent serious adverse events (SAEs), deaths, or any withdrawals due to an AE in this study. The percentage of patients with any TEAE was higher for HOE901-U300 (9/20 [45.0 %]) than for the Lantus treatment (4/20 [20.0%]). However, no TEAEs were classified as related to the IMP. No TEAEs linked to injection site reactions were observed for either treatment. While an accidental overdose of mealtime insulin (Apidra) was reported, no hypoglycemias were associated with this event.

The most frequently reported TEAE was nasopharyngitis (other than hypoglycemic events), with 4 TEAEs reported by 4 patients. Of the 4 TEAEs, 2 were reported following HOE901-U300 and 2 were reported following Lantus. In addition, there were a number of TEAEs classified as gastrointestinal disorders reported by patients during the treatment period in which they received HOE901-U300; 1/20 patients reported a TEAE of abdominal discomfort, 1/20 patients reported a TEAE of dental caries, 1/20 patients reported TEAE of stomatitis, and 1/20 patients reported a TEAE of vomiting. All other TEAEs were reported by 1 patient only.

During the on-treatment period, 17/20 patients (85.0%) experienced at least 1 hypoglycemic event for the HOE901-U300 treatment and 20/20 patients (100%) for the Lantus treatment (Table 1). In addition, the total number of reported hypoglycemic events was slightly lower for the HOE901-U300 treatment than the Lantus treatment, with 126 and 192 events reported, respectively (Table 2). Of these hypoglycemic events, 6 were reported as nocturnal (00:00 to 05:59) during HOE901-U300 treatment with 20 nocturnal events reported during Lantus treatment.

There were a low number of PCSAs reported during the study for laboratory parameters, vital signs, and ECG parameters, but none were considered to be clinically significant and there were no relevant differences between HOE901-U300 and Lantus treatments.

Table 1-Number (%) of patients with at least one hypoglycemia event during the on-treatment period-safety population

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)	
	HOE901-U300 (N=20)	Lantus (N=20)	HOE901-U300 (N=20)	Lantus (N=20)
Any hypoglycemia event	17 (85.0%)	20 (100%)	4 (20.0%)	8 (40.0%)
Documented symptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	14 (70.0%)	18 (90.0%)	3 (15.0%)	7 (35.0%)
<3.0 mmol/L (54 mg/dL)	8 (40.0%)	12 (60.0%)	1 (5.0%)	4 (20.0%)
Asymptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	10 (50.0%)	13 (65.0%)	2 (10.0%)	2 (10.0%)
<3.0 mmol/L (54 mg/dL)	2 (10.0%)	3 (15.0%)	0	0
Relative hypoglycemia				
>3.9 mmol/L (70 mg/dL)	0	1 (5.0%)	0	0
Severe and/or confirmed[a] hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	17 (85.0%)	20 (100%)	4 (20.0%)	8 (40.0%)
<3.0 mmol/L (54 mg/dL)	8 (40.0%)	12 (60.0%)	1 (5.0%)	4 (20.0%)

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[a]: Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose≤3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L [54 mg/dL])

Table 2-Number of events with at least one hypoglycemia event during the on-treatment period-safety population

Type of hypoglycemia event	All hypoglycemia HOE901-U300 (N=20)	All hypoglycemia Lantus (N=20)	Nocturnal hypoglycemia (00:00-05:59) HOE901-U300 (N=20)	Nocturnal hypoglycemia (00:00-05:59) Lantus (N=20)
Any hypoglycemia event	126	192	6	20
Documented symptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	75	142	3	18
<3.0 mmol/L (54 mg/dL)	24	40	1	6
Asymptomatic hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	51	47	3	2
<3.0 mmol/L (54 mg/dL)	4	4	0	0
Relative hypoglycemia				
>3.9 mmol/L (70 mg/dL)	0	3	0	0
Severe and/or confirmed[a] hypoglycemia				
≤3.9 mmol/L (70 mg/dL)	126	189	6	20
<3.0 mmol/L (54 mg/dL)	28	44	1	6

[a]: Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose≤3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L [54 mg/dL])

Pharmacokinetic results:

The mean (± SD) trough serum insulin concentrations for the 2 treatments was 33.1 ± 21.7 µU/mL for HOE901-U300 and 31.7 ± 27.0 µU/mL for Lantus, which did not differ greatly from the baseline value of 32.6 ± 16.8 µU/mL.

Issue date: 07-Jul-2014