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 / Company: Sanofi Drug substance(s): HOE901-U300 (insulin glargine)	Study Identifiers: NCT01689129, UTN U1111-1130-3513 Study code: EFC12449
Title of the study: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Japanese Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period (EFC12449 6-months)	
Study center(s): Multicenter (22 centers in Japan)	
Study period: Date first patient enrolled: 02/Oct/2012 Date last patient completed: 02/Oct/2013	
Phase of development: Phase 3	

Objectives:

Primary objective: To compare the efficacy of HOE901-U300 and Lantus in terms of change of glycated hemoglobin A1c (HbA_{1c}) from baseline to endpoint (scheduled at Month 6 [Week 26]) in patients with type 1 diabetes mellitus (T1DM).

Secondary objectives:

- To compare HOE901-U300 and Lantus in terms of change from baseline to endpoint (Month 6 [Week 26]) in fasting plasma glucose (FPG), pre-basal insulin injection plasma glucose, mean plasma glucose (8-point self-monitored plasma glucose [SMPG] profile) and variability of preinjection plasma glucose;
- To compare HOE901-U300 and Lantus in terms of reaching target HbA_{1c} values;
- To compare HOE901-U300 and Lantus in terms of occurrence of hypoglycemia;
- To assess the safety and tolerability of HOE901-U300 including development of anti insulin antibodies (AIA);
- To compare HOE901-U300 and Lantus in terms of treatment satisfaction of patients using the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Exploratory objective of the continuous glucose monitoring (CGM) substudy:

- To confirm the 24-hour glycemic profile in CGM of HOE901-U300 and Lantus in a subset of 30 eligible patients.

Methodology: This was a multicenter, open-label, randomized, 2-arm parallel-group, comparative Phase 3 outpatient study, in patients with T1DM who had been on a basal plus mealtime insulin regimen for at least one year. Randomization was 1:1 (HOE901-U300 versus Lantus) and was stratified according to HbA_{1c} values at screening (<8.0%; ≥8.0).

Number of patients:	Planned: 240 (120 per treatment arm), Randomized: 243 Treated: 243	Planned CGM: 30
Evaluated:		
	Efficacy: 243	
	Safety: 243	
	CGM: 29	

Diagnosis and criteria for inclusion:

Inclusion criteria: Adult patients with T1DM; signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; less than 1 year history of basal plus mealtime insulin; current insulin not stable in the 30 days prior to screening; severe hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months before screening visit.

Study treatments

Investigational medicinal products (IMPs): Tested drug - HOE901-U300; Control drug - HOE901-U100 (Lantus)

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution in a glass cartridge that has been assembled in a pen-injector (reusable modified Tactipen). Lantus (insulin glargine 100 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution supplied in the marketed disposable Solostar® pen.

Route(s) of administration: subcutaneous injection

Dose regimen: Once daily injection in the evening, which was defined as the time period from immediately prior to the evening meal until bedtime. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

Starting dose: Patients on Lantus or neutral protein Hagedorn (NPH) or insulin detemir once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to the total daily basal insulin dose on the day prior to the baseline visit.

Patients on NPH or insulin detemir more than once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was to be 20% less than the total daily basal insulin dose on the day prior to the baseline visit.

The basal insulin dose was adjusted once weekly to achieve fasting SMPG in the target range of 4.4 to 7.2 mmol/L (80 to 130 mg/dL); glycemic targets could be adapted for individual patients, if deemed necessary:

- Increase by at least 10% of the daily dose if fasting, preprandial plasma glucose was greater than 7.2 mmol/L (130 mg/dL) and there had been no evidence of relevant hypoglycemia, in the range:
  - +1.5 U (minimum possible dose increment) to 4.5 U for HOE901-U300
  - +1 U (minimum possible dose increment) to 4 U for Lantus
- If SMPG was <4.4 mmol/L (<80 mg/dL) or if relevant hypoglycemia occurred, the dose was adjusted at the Investigator's discretion as follows:
  - 1.5 U (minimum possible dose increment) for HOE901-U300
  - 1 U (minimum possible dose increment) for Lantus
- If SMPG was <3.3 mmol/L (<60 mg/dL) or a case of severe hypoglycemia (requiring 3rd party assistance) was reported without an adequate explanation (eg, omission of a meal or heavy exercise) for the event, upward titration was stopped for one week, and dose decreased at the Investigator's discretion.

Noninvestigational medicinal product(s): Mandatory background therapy (short-acting mealtime insulin analog: glulisine, aspart or lispro, not regular human insulin).

Patients in both treatment groups were to continue with their short-acting mealtime insulin analog during the study. Mealtime insulin analog doses were to be adjusted to optimize glycemic control after basal insulin doses had been optimized. Bolus insulin doses could be reduced while basal insulin doses were increased to avoid daytime hypoglycemia.

Duration of treatment: Up to 12 months

Duration of observation: Up to 58 weeks (up to 2-week screening period + 6-month efficacy and safety period + 6-month safety extension period + 4 weeks of posttreatment follow-up).

The analysis period for efficacy and safety is the main 6-month on-treatment period. Results presented in this clinical study report refer to this period.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: change in HbA_{1c} from baseline to endpoint (Month 6).

Secondary endpoints: proportion of patients (%) with HbA_{1c} <7% and ≤6.5% at endpoint (Month 6), change from baseline to endpoint (Month 6) in: FPG; pre-injection SMPG; variability of pre-injection SMPG; 8-point SMPG; mean 24-hour SMPG; change in variability in mean 24-hour SMPG; daily basal insulin dose, daily mealtime insulin dose and daily total insulin dose (basal+mealtime).

Exploratory secondary endpoints: Proportion (%) of patients with FPG <5.6 mmol/L (100 mg/dL) and proportion of patients (%) with FPG <7.2 mmol/L (130 mg/dL) at endpoint (Month 6); change from baseline to endpoint (Month 6) in 7-point SMPG, average and change in variability in 7-point SMPG; 5-point SMPG, mean fasting SMPG, change from baseline to endpoint (Month 6) in plasma free fatty acids (FFA).

Other: Change in DTSQ from baseline to endpoint (Month 6) measured by change in DTSQs (status version) from baseline to Month 6 and DTSQc (change version) at Month 6: satisfaction with treatment, perceived hyperglycemia, and perceived hypoglycemia.

Exploratory CGM:

CGM primary endpoint: area under the curve (AUC) mean of 24 hours

CGM secondary endpoints: AUC_{mean} (AUC_{mean_noc} and $AUC_{mean\_daytime}$), AUC_{value} (AUC_{value_24h}, AUC_{value_noc} and $AUC_{value\_daytime}$), mean of daily difference (MODD), parameter from target blood glucose (TBG) range (80-140 mg/dL), and hyperglycemic index, hypoglycemic index and index of glycemic control (ICG).

Safety: Hypoglycemia; injection site reactions; hypersensitivity reactions; cardiovascular events and the subset that are major cardiovascular events (MACE); adverse events of special interest (AESI) with immediate notification (ie, increase in alanine aminotransferase (ALT), pregnancy, symptomatic overdose with IMP/nonIMP); AESIs without immediate notification (ie, asymptomatic overdose); treatment-emergent adverse events (TEAEs), TEAEs leading to death, serious adverse events (SAEs) and TEAEs leading to withdrawal of study treatment; other safety information including clinical laboratory data, vital signs (including body weight), 12-lead electrocardiogram (ECG) and anti-insulin antibodies (AIA).

Anti-insulin sampling times and bioanalytical methods: Samples for AIA assessment were be collected at baseline (Visit 3), 4 weeks (Visit 7), 12 weeks (Visit 11), 6 months (Visit 14) and 12 months (Visit 18) and in case of premature discontinuation from the study treatment. Anti-insulin antibodies (AIA) were determined at a centralized laboratory using a validated AIA binding assay methodology.

Continuous glucose monitoring sampling times: Interstitial glucose levels were continuously monitored throughout the day and night for up to 72 hours at baseline, at 11 weeks and at 25 weeks. The system used was the Medtronic iPro2® CGM system (Medtronic Japan Co., Ltd, Tokyo), an approved device with single-use disposable electrochemical sensing elements.

Statistical methods: The primary efficacy endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) was analyzed using an analysis of covariance (ANCOVA) model with treatment, strata of screening HbA_{1c} (<8.0 and ≥8.0%) as fixed effects and using the HbA_{1c} baseline value as a covariate. Differences between HOE901-U300 and Lantus and two-sided 95% confidence intervals (CIs) were estimated within the framework of ANCOVA.

A stepwise closed testing approach was used for the primary efficacy endpoint to assess noninferiority and superiority sequentially. Step 1 assessed noninferiority of HOE901-U300 versus Lantus. To assess noninferiority, the upper bound of the 2 sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus was compared with a predefined non inferiority margin of 0.4% HbA_{1c}. Noninferiority would be demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901 U300 and Lantus on the modified intention-to-treat (mITT) population is <0.4%. Step 2 assessed superiority of HOE901-U300 versus Lantus only if noninferiority was demonstrated. The superiority of HOE901-U300 over Lantus was demonstrated if the upper bound of the two-sided 95%CI of the difference between HOE901-U300 and Lantus on mITT population was <0. The test for the primary endpoint was performed one sided at level $\alpha = 0.025$.

All continuous secondary efficacy variables (except for changes in variability of the 24-hour mean plasma glucose and variability of pre-injection plasma glucose) were analyzed using a similar ANCOVA model to the primary efficacy analysis. This model included treatment, randomization strata of screening HbA1c (<8.0 and ≥8.0%) as fixed effects, and the corresponding baseline value as a covariate. For change in variability, an analysis of variance model with treatment, and randomization strata of screening HbA_{1c} (<8.0 and ≥8.0%) as fixed effects was used. The categorical secondary efficacy variables were analyzed using a Cochran Mantel Haenszel (CMH) method stratified on randomization strata providing relative risk estimates and corresponding 95% CIs.

Safety analyses were descriptive, based on the safety population.

Summary: The current report presents the efficacy and safety results for the main 6-month on-treatment period.

Population characteristics: A total of 243 patients with T1DM were randomized to HOE901-U300 (n=122) or to Lantus (n=121); 243 patients were exposed to IMP (safety population). The mITT population (efficacy population) and safety population included 243 patients. Of 30 patients who signed the informed consent to enter the CGM substudy, 29 were included in the CGM population.

A similar percentage of patients in each treatment group discontinued the study treatment prematurely (HOE901-U300: 5/122, 4.1%; Lantus: 4/121, 3.3%). A total of 117/122 (95.9%) patients in HOE901-U300 group and 117/121 (96.7%) patients in Lantus group completed the main 6-month on-treatment period.

Demographics and baseline characteristics were well-balanced between the 2 treatment groups. The mean age of the study population was 45.2 years, 23/243 (9.5%) were ≥ 65 years. The mean BMI at baseline was 23.5 kg/m². The mean duration of T1DM prior to study start was 13.0 years; the mean duration of prior treatment with basal insulin was 9.78 years; and the mean total daily insulin dose at baseline was 46.4 U (0.735 U/kg). Within 7 days prior to randomization, most patients received insulin glargine as basal insulin (90.1%), followed by insulin detemir (9.5%), and NPH (0.4%).

Mean HbA_{1c} at baseline was similar in both treatment groups (HOE901-U300: 8.06% and Lantus: 8.08%; for randomized patients).

Efficacy results:

Primary endpoint:

The LS mean change in HbA_{1c} from baseline to endpoint (Month 6) was -0.30% (95% CI [-0.411 to -0.183]) in the HOE901-U300 treatment group and -0.43% (95 %CI [-0.542 to -0.313]) in the Lantus treatment group. Noninferiority of HOE901-U300 versus Lantus was demonstrated as shown by the upper bound of the 95%CI below the predefined noninferiority margin of 0.4% (LS mean difference in HbA1c versus Lantus was 0.13%; 95 % CI [-0.029 to 0.291]). Superiority of HOE901-U300 versus Lantus was not demonstrated.

Secondary endpoints:

The percentage of patients who reached the HbA_{1c} target <7% at Month 6 was 15.6% (19/122) in HOE901-U300 group and 20.0% (24/120) in Lantus group. The percentage of patients who reached this target at Month 6 without any episode of severe and/or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia during the last 3 months of the main 6-month on-treatment period was 5.7% (7/122) in the HOE901-U300 group and 2.5% (3/120) in the Lantus group. The results were consistent when considering patients with target HbA_{1c} <7% at Month 6 and no nocturnal (00:00 – 05:59) severe and/or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia during the last 3 months: 13.9% (17/122) on HOE901-U300 and 13.3% (16/120) on Lantus.

The LS mean change in fasting plasma glucose (FPG) from baseline to endpoint (Month 6) was -0.75 mmol/L in the HOE901-U300 group and -1.15 mmol/L in Lantus group. Decreases in FPG from baseline to endpoint (Month 6) were similar in both treatment groups (LS mean difference versus Lantus was 0.41 mmol/L [95% CI: -0.578 to 1.392].

The LS mean change in pre-injection SMPG from baseline to endpoint (Month 6) was divergent between the HOE901-U300 (-0.63 mmol/L) and Lantus (0.40 mmol/L) groups. The LS mean difference between the treatment groups was -1.03 mmol/L (95% CI [-1.778 to -0.278]).

The LS mean decrease in variability of pre-injection plasma glucose from baseline to endpoint (Month 6) was similar in both treatment groups (HOE901-U300: -2.81; Lantus: -2.67). The LS mean difference between the treatment groups was 0.15 (95% CI [-5.851 to 5.555]).

Graphical presentation of the mean 8-point SMPG profiles was similar for HOE901-U300 and Lantus at baseline but divergent at endpoint. The profiles in the HOE901-U300 group showed a decrease in plasma glucose at all time points at Month 6 compared to baseline. The profiles in the Lantus group showed no consistent trend across all the time points at Month 6 compared to baseline. From baseline to Month 6, in both treatment groups, the largest mean decrease occurred in the 2 hour postbreakfast SMPG. The change in 24-hour average plasma glucose, based on 8-point SMPG profile, from baseline to endpoint (Month 6) was greater in the HOE901-U300 group than in the Lantus group (LS mean difference versus Lantus was -0.89 mmol/L [95%CI: -1.451 to -0.332]). The change in variability of 24-hour average plasma glucose, based on 8-point SMPG profile, from baseline to endpoint (Month 6) was similar in both treatment groups (LS mean difference versus Lantus was -1.86 [95%CI: -6.527 to 2.813]).

At endpoint (Month 6), the mean of average daily total insulin dose was 50.73 U (0.79 U/kg) in HOE901-U300 group and 45.96 U (0.74 U/kg) in Lantus group. The mean of average daily basal insulin dose at Month 6 in HOE901-U300 group was 23.03 U (0.35 U/kg) compared to 18.21 U (0.29 U/kg) in Lantus group; The mean of average daily mealtime insulin dose at Month 6 was comparable between two treatment groups (HOE901-U300: 27.99 U [0.44 U/kg]; Lantus: 27.75 U [0.45 U/kg]).

Exploratory efficacy endpoints:

The percentage of patients who reached target FPG <5.6 mmol/L (100 mg/dL) at Month 6 was 12.3% (15/122) in the HOE901-U300 group and 19.7% (23/121) in the Lantus group. The percentage of patients who reached target FPG <5.6 mmol/L (100 mg/dL) at Month 6 with no severe and/or confirmed (<3.0 mmol/L [54 mg/dL]) hypoglycemia during the last 3 months of the main 6-month on-treatment period was 6.6% (8/122) in the HOE901-U300 group and 3.4% (4/121) in the Lantus group.

Results of the analyses based on 7-point and 5-point SMPG profiles were consistent with those based on 8-point SMPG profiles. At Month 6, a similar average prebreakfast SMPG was reached in both groups (HOE901 U300: 7.94 mmol/L; Lantus: 7.65 mmol/L).

The decrease in plasma concentration of FFA from baseline to Month 6 was similar in both treatment groups (LS mean -0.10 mmol/L in the HOE901-U300 group and -0.11 mmol/L in the Lantus group).

The overall satisfaction of the patients with treatment in both treatment groups measured by DTSQs and DTSQc was good throughout the study. The positive mean DTSQc Total Treatment Satisfaction scores represent improvements in both treatment groups but with a greater improvement in the HOE901-U300 group than in the Lantus group.

CGM endpoint:

The mean CGM profile at Month 6 suggests similar glucose excursions over time in the HOE901-U300 and Lantus groups. Mean AUC_{mean_24h} and mean $AUC_{mean\_daytime}$ in 2nd day of CGM terms at Month 6 was decreased compared to baseline in both groups. The point estimate of the treatment ratio of AUC_{mean_24h} was 1.04 [95%CI: 0.68 to 1.58]. The point estimate of the treatment ratio of $AUC_{mean\_daytime}$ was 1.12 [95%CI: 0.74 to 1.68]. Mean AUC_{mean_noc} (2nd day of CGM) value at Month 6 decreased in the HOE901-U300 group and increased in the Lantus group; the point estimate of the treatment ratio was 0.87 [95%CI: 0.45 to 1.69]. Mean duration of TBG (80 to 140 mg/dL) in 2nd day of CGM terms at Month 6 was longer compared to baseline in both groups and more pronounced in the Lantus group. The point estimate of the treatment ratio was 0.77 [95%CI: 0.49 to 1.22].These findings might be related to differences in the treatment response in both groups based on the changes of HbA_{1c} at Month 6 from baseline, ie, HbA_{1c} decreased from baseline in a lower proportion of patients in the HOE901-U300 group compared to in the Lantus group (55.5% versus 93.9% subjects). Mean decrease of MODD from baseline to Month 6 was more remarkable in the HOE901-U300 group (-16.44) than in the Lantus group (-7.37), suggestive of reduced inter-daily glycemic variability in the HOE901-U300 group compared to the Lantus group.

Safety results:

Overall, hypoglycemia was reported by the same percentages of patients in both treatment groups (HOE901-U300: 119/122 [97.5%]; Lantus: 118/121 [97.5%]). The overall nocturnal hypoglycemia was reported by a lower percentage of patients in HOE901-U300 group than in Lantus group (85/122 [69.7%] versus 98/121 [81.0%]).

The incidence of patients reporting nocturnal hypoglycemia (severe and/or confirmed by SMPG ≤3.9 mmol/L [70 mg/dL]) reported between 00:00 and 05:59 hours occurring between baseline and endpoint (Month 6) was 68.9% (84/122) in the HOE901-U300 group and 81.0% (98/121) in the Lantus group (RR of 0.85 [95%CI: 0.73 to 0.99]).

A 13% risk reduction in favor of HOE901-U300 was observed for severe and/or confirmed hypoglycemia (<3.0 mmol/L [54 mg/dL]) over the main 6-month on-treatment period. Risk reductions in favor of HOE901-U300 were also observed for documented symptomatic nocturnal hypoglycemia (≤3.9 mmol/L [70 mg/dL] and <3.0 mmol/L [54 mg/dL]: 23% and 36% reductions) and severe and/or confirmed nocturnal hypoglycemia (≤3.9 mmol/L [70 mg/dL] and <3.0 mmol/L [54 mg/dL]: 15% and 31% reductions) over the main 6-month on-treatment period.

During the main 6-month on-treatment period severe hypoglycemia was reported in 7/122 (5.7%) of HOE901-U300 patients and 12/121 (9.9%) of Lantus patients. Severe nocturnal hypoglycemia was reported by 2/122 (1.6%) patients in the HOE901-U300 group and 1/121 (0.8%) patient in the Lantus group. Severe hypoglycemia was confirmed by the Severe Hypoglycemia Review Board for 16 events in 6/122 (4.9%) patients (0.27 events per patient-year) in the HOE901-U300 group and 9 events in 8/121 (6.6%) patients (0.15 events per patient-year) in the Lantus group.

The percentages of patients with any TEAEs (HOE901-U300: 76/122 [62.3%]; Lantus: 78/121 [64.5%]) were similar between two groups. The same proportion of patients experienced serious TEAEs in both treatment groups (HOE901-U300: 3/122 [2.5%]; Lantus: 3/121 [2.5%]).

No death was observed in both treatment groups during the main 6-month on-treatment period.

One patient (0.8% [1/122]) experienced TEAEs leading to permanent treatment discontinuation due to spinal column stenosis in HOE901-U300 compared with no patients who reported TEAEs leading to permanent treatment discontinuation in Lantus group.

One patient in HOE901-U300 group experienced nonserious moderate ALT increased.

Symptomatic overdose with IMP was reported by 1 patient in HOE901-U300 group. Asymptomatic overdose with IMP was reported by 1 patient in HOE901-U300 group and 2 patients in Lantus group.

No events of MACE, injection site reactions, malignancy, or pregnancy was reported during the main 6-month on-treatment period in either treatment group. Hypersensitivity reactions during the main 6-month on-treatment period were reported by a lower percentage in HOE901-U300 group than in Lantus group (HOE901-U300: 6.6% [8/122]; Lantus: 11.6% [14/121]).

In both treatment groups, there was no apparent change in body weight from baseline to the last main 6-month on-treatment value (HOE901-U300: -0.11 kg; Lantus: 0.46 kg).

There was no difference between treatment groups in terms of the incidence of patients with AIA, AIA titer, and cross-reactivity to human insulin. In AIA positive patients, there was a smaller HbA_{1c} reduction in the HOE901-U300 group than compared to the Lantus group. There were no other treatment differences concerning the effect of AIA on efficacy and safety endpoints.

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Sponsor / Company: Sanofi Drug substance(s): HOE901-U300 (insulin glargine)	Study Identifiers: NCT01689129, UTN U1111-1130-3513 Study code: EFC12449
Title of the study: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Japanese Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period (EFC12449-12-months)	
Study center(s): Multicenter (22 centers in Japan)	
Study period: Date first patient enrolled: 02/Oct/2012 Date last patient completed: 30/Apr/2014	
Phase of development: Phase 3	

Objectives: The primary and secondary objectives of the study (described below) were based on the main 6-month on-treatment period, the results of which were reported in an earlier clinical study report (CSR). Efficacy and safety variables used to evaluate the study objectives were also measured over the 12-month on-treatment period and are described in this CSR. The 6-month comparative extension period was designed to evaluate the maintenance of efficacy and safety of HOE901-U300 (insulin glargine 300 U/mL) in comparison with Lantus.

Primary objective: To compare the efficacy of HOE901-U300 and Lantus in terms of change in glycated hemoglobin A1c (HbA_{1c}) from baseline to endpoint (scheduled at Month 6 [Week 26]) in patients with type I diabetes mellitus (T1DM).

Main secondary objective:

- To compare HOE901-U300 and Lantus in terms of change from baseline to endpoint (Month 6) in fasting plasma glucose (FPG), pre-injection (pre-basal insulin) plasma glucose, mean plasma glucose (8-point self-monitored plasma glucose [SMPG] profile) and variability of plasma glucose.

Further secondary objectives:

- To compare HOE901-U300 and Lantus in terms of reaching target HbA_{1c} values;
- To compare HOE901-U300 and Lantus in terms of occurrence of hypoglycemia;
- To assess the safety and tolerability of HOE901-U300 including development of anti-insulin antibodies (AIAs);
- To compare HOE901-U300 and Lantus in terms of treatment satisfaction.

Following Month 12, after the end of the safety extension period, patients completed a follow-up visit 2 days after completing study treatment or were invited to continue in the study (following separate consent) for a further month (Month 13). The objective of the follow-up period was to monitor patient safety and efficacy during the initial period after changing from investigational medicinal product (IMP) (HOE901-U300 or Lantus) to commercial basal insulin.

Methodology: The randomization was 1:1 (HOE901-U300 versus Lantus) and was stratified according to HbA_{1c} values at screening (<8.0%; ≥8.0%). The sample size (120 with HOE901-U300 and 120 with Lantus) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) as well as to allow conclusions on the first main secondary endpoint (FPG, pre-injection [pre-basal insulin] plasma glucose, 8-point SMPG profile, and plasma glucose variability) for the initial 6-month on-treatment period.

Results based on the main 6-month on-treatment period, including the primary efficacy analysis which tested the noninferiority of HOE901-U300 compared to Lantus in terms of change of HbA_{1c} from baseline to endpoint (Month 6), were reported in an earlier CSR.

Number of patients:	Planned: 240 (120 per treatment arm)
	Randomized: 243 (HOE901-U300: 122; Lantus: 121)
	Treated: 243
Evaluated:	
	Efficacy: 243
	Safety: 243

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with T1DM as defined by World Health Organization; signed written informed consent.

Key exclusion criteria: Age <18 years; night shift workers; HbA_{1c} <7.0% or >10% at screening; less than 1 year on basal plus mealtime insulin; use of premix insulins, human regular insulin as mealtime insulin and/or any glucose-lowering drugs other than basal insulin and mealtime rapid-insulin analogue in the last 3 months before screening visit; use of an insulin pump in the last 6 months before screening visit and/or plan to switch to insulin pump in next 12 months; any contraindication to use of insulin glargine as defined in the Japanese product labeling; not willing to inject insulin glargine as assigned by the randomization process once daily in the evening; severe hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months before screening visit; weight change of ≥5 kg during the last 3 months prior to screening visit; last ophthalmologic examination >12 months prior to randomization; unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require treatment (eg, laser, surgical treatment or injectable drugs) during the study period.

Study treatments

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

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution supplied in a (reusable) insulin pen (modified TactiPen®). Lantus (insulin glargine 100 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution supplied in the marketed SoloStar® (prefilled ie, disposable pen).

Route(s) of administration: subcutaneous injection

Dose regimen: Once daily injection in the evening, which was defined as the time period from immediately prior to the evening meal until bedtime. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

Starting dose: Patients on Lantus or neutral protein Hagedorn (NPH) once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to total insulin dose in the 3 days prior to the baseline visit.

Patients on NPH more than once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was to be approximately 20% less than the total daily NPH insulin dose in the day prior to the baseline visit.

Noninvestigational medicinal product(s) (NIMPs): Mandatory background therapy (short-acting mealtime insulin analogue and if taken before study start, metformin).

Mealtime insulin doses were to be adjusted to optimize glycemic control after basal insulin doses had been optimized. Bolus insulin doses could be reduced as basal insulin doses were increased. Patients in both treatment groups were to continue with their mealtime insulin analog during the study.

Duration of treatment: Up to 12 months

Duration of observation: Up to 58 weeks (up to 2-week screening period + main 6-month efficacy and safety period + 6-month safety extension period + up to 4 weeks of posttreatment follow-up)

The analysis period for efficacy and safety was the main 6-month on-treatment period and a 12-month on treatment period.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: Change in HbA_{1c} from baseline to Month 6 (main 6-month on-treatment period); descriptive statistics of change in HbA_{1c} for the 12-month on-treatment period from baseline to Month 12 are presented.

Other efficacy endpoints: Change from baseline to Month 12 for the following: FPG, SMPG (including pre-injection SMPG, variability of pre-injection SMPG, 7-point SMPG profiles, fasting (pre breakfast) SMPG, and mean plasma glucose based on 4-point SMPG profiles), daily average insulin doses (including basal, mealtime insulin and total), insulin dose by visit and other laboratory endpoints (including free fatty acid (FFA) and C-peptide). Assessment of treatment satisfaction using Diabetes Treatment Satisfaction Questionnaire (DTSQs) up to Month 12.

Efficacy evaluated for the 4-week follow-up period included change from baseline and follow-up baseline (Month 12) to Month 13 in: daily average fasting (pre breakfast) SMPG and average SMPG values based on 5-point SMPG profiles, and daily average insulin doses (including basal, mealtime and total dose) by visit (by week between Month 12 and 13 visits).

Safety:

The safety analysis was based on all events of hypoglycemia (symptomatic, asymptomatic, severe, probable, relative); local tolerability at injection site, hypersensitivity reactions, adverse events of special interest (AESIs) with immediate notification (ie, increase ALT, pregnancy, symptomatic overdose with IMP/NIMP); AESIs without immediate notification (ie, asymptomatic overdose with IMP/NIMP); other adverse events (AEs) or serious adverse events (SAEs); other safety information including: clinical laboratory data, vital signs including body weight, 12-lead electrocardiogram (ECG) and AIA results.

Safety evaluated for the 4-week follow-up period included hypoglycemia events and AEs.

Anti-insulin antibody sampling times and bioanalytical methods:

Samples for AIA assessment were collected at baseline (Visit 3), Week 4 (Visit 7), Week 12 (Visit 11), Week 26 (Visit 14) and Week 52 (Visit 18) and in case of premature discontinuation from the study treatment. Anti-insulin antibodies were determined at a centralized laboratory using a validated AIA binding assay methodology.

Statistical methods:

Descriptive statistics on the 12-month on-treatment period were provided for HbA_{1c} and other efficacy endpoints for the modified intention to treat (mITT) population.

The efficacy analyses were also conducted on the 4-week follow-up population during the 12-month on-treatment period as well as for the 4-week follow-up period.

Summaries of safety and tolerance results were presented by treatment group (HOE901-U300 or Lantus) for the 12-month on treatment period and during the posttreatment period for both the safety and 4-week follow-up populations. Unless otherwise specified, the analysis of the safety variables is descriptive and no systematic testing was planned.

Summary: The current report presents the efficacy and safety results for the 12-month on-treatment period as well as the 4-week follow-up period.

Population characteristics:

A total of 243 patients with T1DM were randomized to HOE901-U300 (122 patients) or to Lantus (121 patients); 243/243 were exposed to IMP (safety population). The mITT population (efficacy population) included 243 patients.

Overall, a comparable percentage of patients in each treatment group discontinued the study prematurely (HOE901-U300: 6.6% [8/122]; Lantus, 5.8% [7/121]).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 45.2 years; 23 of 243 [9.5%] were ≥65 years. Overall, 46.1% [112/243] of the patients were male. The mean body mass index (BMI) at baseline was 23.5 kg/m^2 (23.8 kg/m^2 in the HOE901-U300 and 23.2 kg/m^2 in the Lantus group). At baseline, 4.9% [12/243] of patients had a BMI ≥30 kg/m^2 and 2.1% [5/243] of patients had renal impairment with an estimated GFR<60 mL/min/1.73 m^2.

Efficacy results:

Mean HbA_{1c} was similar at baseline in both treatment groups. Mean HbA_{1c} decreased from baseline to Month 12 endpoint in both treatment groups; the greatest decrease occurred during the first 12 weeks of treatment. During the extension period, HbA_{1c} tended to increase in both treatment groups, although more in the Lantus group than HOE901-U300 group. At Month 12 endpoint, mean HbA_{1c} was 7.86% in the HOE901-U300 group and 7.82% in the Lantus group. The mean change in HbA_{1c} from baseline to Month 12 endpoint was -0.20% (95% CI: -0.35 to -0.06) in the HOE901-U300 group and -0.25% (95% CI: -0.38 to -0.12) in the Lantus group.

Mean average pre-injection SMPG was similar at baseline in both treatment groups. Average pre-injection SMPG decreased in the HOE901-U300 group from baseline to Month 12, while it increased in the Lantus group. Mean 7-point SMPG profiles were similar at baseline in both treatment groups. At Month 12, 7-point SMPG profiles had improved in both treatment groups at time-points in the morning, ie, pre breakfast, post breakfast, pre lunch and post lunch and tended to increase at time points in the afternoon and evening (pre dinner to bedtime).

Mean average fasting (pre breakfast) SMPG decreased from baseline to Month 12 in both treatment groups; the greatest decrease occurred during the first 4 weeks of treatment in the Lantus group and in the first 6 months in the HOE901-U300 group. Thereafter, mean average pre breakfast SMPG remained relatively stable and was higher in the HOE901-U300 group compared to the Lantus group up to Month 12.

Mean FPG decrease from baseline to Month 12 was greater in the HOE901-U300 group than in the Lantus group. In both treatment groups most of the decrease occurred between baseline and Month 6. The lowest mean FPG was at Month 9 in the HOE901-U300 group and at Month 6 in the Lantus group.

These changes in glycemic control were observed while the basal insulin doses in both treatment groups were increased, primarily during the first 12 weeks and to a greater extent in the HOE901-U300 group than in the Lantus group. Mean daily basal insulin increased gradually from Week 12 to Month 12 in the HOE901-U300 group and decreased gradually in the Lantus group. Mealtime insulin doses were comparable throughout the study with a small increase during the first 2 weeks in both treatment groups. Thereafter, the mealtime dose remained relatively stable until Month 12. At Month 12, the mean daily mealtime insulin dose was 28.53 U (0.45 U/kg) in the HOE901-U300 group, ie, lower than in the Lantus group, where the dose was 29.15 U (0.47 U/kg). From baseline to Month 12, the mean daily mealtime insulin dose increased by 2.49 U (0.04 U/kg) in the HOE901-U300 group and by 5.10 U (0.08 U/kg) in the Lantus group. The mean daily total insulin dose at Month 12 was higher in the HOE901-U300 group than in the Lantus group.

The overall satisfaction of the patients with treatment in both treatment groups measured by DTSQs was good and similar throughout the study.

Safety results:

Overall, during the 12-month on-treatment period, hypoglycemic events occurring any time of the day were reported by comparable percentages of patients (98.4% in HOE901-U300 versus 97.5% in the Lantus group) and nocturnal hypoglycemia with onset between 00:00 and 05:59 hours was reported by a lower percentage of patients in the HOE901-U300 group (80.3%) compared with the Lantus group (85.1%) depending on the category of hypoglycemia. The rate of hypoglycemia events per patient year (any category) was lower in the HOE901-U300 group than in the Lantus group. Severe hypoglycemia was reported by a similar percentage of patients in the HOE901-U300 group and in the Lantus group (9.8% versus 9.1%). Severe nocturnal hypoglycemia (00:00 to 05:59) was reported by 3 patients (2.5%) in the HOE901-U300 group and 1 patient (0.8%) in the Lantus group during the 12-month on-treatment period.

The percentage of patients experiencing TEAEs, serious TEAEs or TEAEs leading to treatment discontinuation during the 12-month on-treatment period was similar in the HOE901-U300 and Lantus groups. TEAE with a fatal outcome was reported in 1 patient (0.8%) in the Lantus group. The patient experienced an SAE of metastases to liver which resulted in death. The Investigator considered the event to possibly be related to the IMP and the NIMP given that the patient received insulin glargine before study enrollment. Seven patients (5.7%) in the HOE901-U300 group and 9 patients (7.4%) in the Lantus group had at least 1 serious TEAE during the 12-month on-treatment period. The most frequently reported serious TEAEs were from the SOC Nervous system disorders mainly due to neurological disorders.

Hypersensitivity reactions were found in 16 patients (13.1%) in the HOE901-U300 group and 20 patients (16.5%) in the Lantus group.

No injection site reactions were reported in any patient in either treatment group.

The laboratory parameters and vital sign data as well as the assessment of ECG readings did not reveal any specific safety concerns during the 12-month on-treatment period.

There was no difference in the immunogenicity profiles between the HOE901-U300 and Lantus treatment groups in terms of AIA status, AIA titer, and cross-reactivity to human insulin, nor was there any difference concerning the effect of AIA on efficacy and safety endpoints.

Overall, no new safety signals were detected in this study in relation to insulin glargine, regardless of the formulation used.

4-week follow-up period:

A total of 215/243 (88.5%) randomized patients (108/122 patients [88.5%] in the post HOE901-U300 group and 107/121 patients [88.4%] in the post Lantus group) participated in the 4-week follow-up period after the end of treatment with IMP. At the end of the 12-month on-treatment period with HOE901-U300 or Lantus, patients were switched to a commercial insulin regimen of Lantus 84/108 patients (77.8%) and 88/107 patients (82.2%) in the post HOE901-U300 and post Lantus groups, respectively.

There were no significant changes in basal insulin doses in both posttreatment groups during the 4-week of follow-up period. In both groups, mealtime insulin dose levels remained unchanged up to the end of the 4-week follow-up period.

In patients previously treated with HOE901-U300 there was a small decrease of fasting (pre breakfast) SMPG in the first week of the follow-up period and a small increase in patients previously treated with Lantus. Thereafter, up to the end of the 4-week follow-up period, in both treatment groups fasting (pre breakfast) SMPG was maintained at a comparable level.

Following the switch to commercial basal insulin (primarily Lantus), increased hypoglycemia was reported in the post HOE901-U300 group. The hypoglycemia events were mostly reported during daytime between 06:00 and 23:59 hours, although the increase was particularly marked for nocturnal hypoglycemia. Severe hypoglycemia was reported in 2 patients (1.9%) in the post HOE901-U300 group and 3 patients (2.8%) in the post Lantus group during the 4-week follow-up period.

Reports of posttreatment AEs in the 4-week follow-up population were comparable in the post HOE901-U300 and post Lantus groups and did not suggest a safety concern.

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