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: NCT01689142, UTN U1111-1130-3649 Study code: EFC12512
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® Both in Combination with Oral Antihyperglycemic Drug(s) in Japanese Patients with Type 2 Diabetes Mellitus with a 6 Month Safety Extension Period (EFC12512 6-months)	
Study center(s): 31 centers in Japan	
Study period: Date first patient enrolled: 21/Sep/2012 Date last patient completed: 07/Nov/2013	
Phase of development: Phase 3	

Objectives:

The primary objective of this study was to compare the efficacy of HOE901-U300 and Lantus in terms of change of glycated hemoglobin A_{1c} (HbA_{1c}) from baseline to endpoint (scheduled at Month 6 [Week 26]) in patients with type 2 diabetes mellitus (T2DM).

Secondary objectives:

- 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-measured plasma glucose [SMPG] profile), and variability of 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 (status, DTSQs) and (change, DTSQc).

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

- To confirm the 24-hour glycemic profile in CGM of HOE901-U300 and Lantus.

Methodology:

This was a multicenter, randomized, open-label, 2-arm parallel-group, comparative Phase 3 outpatient study in patients with T2DM who had been on basal insulin in combination with oral antihyperglycemic drug(s) (OADs) treatment for at least 6 months before screening. The randomization was 1:1 (HOE901-U300 versus Lantus) and was stratified according to HbA_{1c} values at screening (<8.0%; ≥8.0%) and treatment with sulfonylurea or glinide at screening (yes; no). A subset of approximately 30 eligible patients were enrolled in a substudy using CGM, to examine the diurnal glucose patterns produced prior to and after the administration of the investigational medicinal product (IMP).

Number of patients:	Planned: 240 (120 per treatment arm), in main study; 30 in CGM substudy	
	Main study: Randomized: 241	Treated: 240
Evaluated:	Main study: Efficacy: 240	Safety: 240
	CGM substudy: 27	

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with T2DM diagnosed for at least 1 year and treated with basal insulin in combination with OAD(s) for at least 6 months; signed written informed consent. Key exclusion criteria: HbA_{1c} <7.0% or >10% at screening; less than 6 months on basal plus OAD(s) and self-monitoring of blood glucose; use of premix insulin or insulin detemir at 2 times or more a day, or glucagon-like peptide 1 receptor agonists in the last 3 months, or an insulin pump within the last 6 months; use of mealtime insulin (rapid-acting insulin analogue and short-acting insulin) for more than 10 days in the last 3 months before screening visit; severe hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months before screening visit.

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 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 5.6 mmol/L (80 to 100 mg/dL). Best efforts were made to reach the target range by 8 to 12 weeks post-randomization; glycemic targets could be adapted for individual patients, if deemed necessary:

- By +1.5 U for HOE901-U300 or +1 U for Lantus, if the median fasting SMPG of last 3 days was in the range of >5.6 and <7.8 mmol/L (>100 mg/dL and <140 mg/dL)
- By +3 U for HOE901-U300 or +2 U for Lantus, if the median fasting SMPG of last 3 days was ≥7.8 mmol/L (≥140 mg/dL)
- By -3 U for both HOE901-U300 and Lantus, if the median fasting SMPG of last 3 days was in the range of ≥3.3 and <4.4 mmol/L (≥60 mg/dL and <80 mg/dL)
- By -3 U for both HOE901-U300 and Lantus or at the discretion of the Investigator, if the median of fasting SMPG of the last 3 days was <3.3 mmol/L (<60 mg/dL) or occurrence of >2 symptomatic or 1 severe hypoglycemia episode in the preceding week.

Non-investigational medicinal product(s): mandatory background therapy (OADs)

Patients in both treatment groups were to continue with OAD(s) during the study as received prior to the study. In the case of 2 or more symptomatic or 1 severe hypoglycemic episode, it was recommended to reduce the dose of sulfonylurea or glinide in patients treated with sulfonylurea or glinide. For patients treated with other OAD(s), the dose was reduced based on the Investigator's best medical judgment.

Rescue treatment

After the titration period (ie, after week 12), if the basal insulin dose adjustment and appropriate other actions failed to decrease FPG/HbA_{1c} under the threshold values of 11 mmol/L (200 mg/dL) for FPG and 8.5% for HbA_{1c} and no apparent reason for insufficient control was identified, intensification of the treatment was to be considered. The choice of the antidiabetic treatment to be added to the basal insulin and oral antihyperglycemic background therapy was based on the Investigator's decision and local labeling documents.

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 post-treatment 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.

For all patients requiring rescue therapy during the 6-month on-treatment period, the last post-baseline efficacy measurement before the start of rescue therapy was used as the efficacy endpoint. These patients were excluded from efficacy analyses after initiation of rescue treatment. For safety endpoints, the analysis period is the main 6-month on-treatment period regardless of the use of rescue therapy.

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; daily basal insulin; pre-injection SMPG; variability of pre-injection SMPG; 8-point SMPG profiles; mean 24-hour SMPG; change in variability in mean 24-hour SMPG; daily basal insulin dose.

Exploratory efficacy endpoints: Proportion (%) of patients with FPG <5.6 mmol/L (100 mg/dL) and proportion of patients (%) with FPG <6.7 mmol/L (120 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; 4-point SMPG, mean fasting SMPG, proportion of patients with rescue therapy, change from baseline to endpoint (Month 6) in plasma free fatty acids (FFA).

Other: change in DTSQs and DTSQc from baseline to endpoint (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 adverse cardiovascular events (MACE); malignancies; adverse events of special interest (AESI) (ie, increase in alanine aminotransferase [ALT], pregnancy, symptomatic overdose with IMP/non-IMP [NIMP], and asymptomatic overdose); treatment-emergent adverse events (TEAEs) leading to death; and adverse events (AEs) leading to withdrawal; and serious adverse events (SAEs); other safety information including clinical laboratory data, vital signs (eg, change in body weight from baseline to endpoint), 12-lead electrocardiogram (ECG), and AIA.

Anti-insulin sampling times and bioanalytical methods: Samples for AIA assessment were 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 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 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 Month 6). 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%) and use of sulfonylurea or glinide (yes, no) 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 two 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 noninferiority 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 α=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 HbA_{1c} (<8.0 and ≥8.0%) and use of sulfonylurea or glinide (yes, no) 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 241 patients with T2DM were randomized to HOE901-U300 (n=121) or to Lantus (n=120); 240 patients were exposed to IMP (safety population). The mITT population (efficacy population) included 240 patients.

Overall, a comparable number of patients in each treatment group discontinued the study treatment prematurely (HOE901-U300: 3/121 [2.5%]; Lantus: 2/120 [1.7%]). A total of 115 (95.0%) patients in the HOE901-U300 group and 118 (98.3%) in the Lantus group completed the main 6-month treatment period (2 patients in HOE901-U300 group who received rescue medication were excluded from the completers population).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 60.8 years, 102/241 (42.3%) were ≥65 years. The mean body mass index at baseline was 25.3 kg/m². The mean duration of T2DM prior to study start was 14.0 years; the mean duration of prior treatment with basal insulin was 2.45 years, and the mean total daily basal insulin dose at baseline was 16.4 U (0.24 U/kg). The majority of patients took insulin glargine (insulin glargine 95.0% versus insulin detemir 5.0%) on the 7 days before start of study treatment; more patients in the HOE901-U300 group were on insulin glargine (98.3%) compared to the Lantus group (91.7%).

Mean HbA_{1c} at baseline was similar in both treatment groups (HOE901-U300: 7.99% and Lantus: 8.06%).

Efficacy results:

Primary endpoint:

The least squares (LS) mean change in HbA_{1c} from baseline to endpoint (Month 6) was similar in both treatment groups (HOE901-U300: -0.45% (95% CI [-0.576 to -0.329]); Lantus: -0.55% (95 %CI [-0.675 to -0.427]). Noninferiority of HOE901-U300 versus Lantus was demonstrated with the LS mean difference in HbA_{1c} versus Lantus of 0.10% (95% CI [-0.075 to 0.272]) with the upper bound lower than the predefined noninferiority margin of 0.4%. Superiority of HOE901-U300 versus Lantus was not demonstrated.

Main secondary efficacy endpoints:

The proportion of patients having reached HbA_{1c} <7% at Month 6 was similar between the 2 treatment groups (HOE901-U300: 25.0% [30/120]); Lantus: 24.2% [29/120]). A similar proportion of patients achieved the target of HbA_{1c} <7% without emergent severe or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia in both treatment groups (HOE901-U300: 23.3%, [28/120]; Lantus: 22.5%, [27/120]). The same proportion of patients achieved the target of HbA_{1c} <7% without nocturnal emergent severe or confirmed hypoglycemia in both treatment groups (23.3%, [28/120]). The proportion of patients having reached HbA_{1c} ≤6.5% was numerically higher in the HOE901-U300 group (11.7% [14/120]) than in the Lantus group (9.2% [11/120]) with a relative risk (RR) of 1.23 (95% CI [0.59 to 2.54]).

The LS mean decrease in FPG from baseline to endpoint (Month 6) was similar between the two treatment groups (HOE901-U300: -1.21 mmol/L; Lantus: -1.25 mmol/L). The LS mean difference between the treatment groups was 0.04 mmol/L (95% CI [-0.403 to 0.488]).

The LS mean increase in pre-injection SMPG from baseline to endpoint (Month 6) was 0.70 mmol/L in the HOE901-U300 group and 0.92 mmol/L in the Lantus group. The LS mean difference between the treatment groups was -0.22 mmol/L (95% CI [-1.021 to 0.574]).

The LS mean increase in variability of pre-injection plasma glucose from baseline to endpoint (Month 6) was numerically higher in the HOE901-U300 group (2.21%) than in the Lantus group (0.04%). The LS mean difference between the treatment groups was 2.17% (95% CI [-1.396 to 5.726]).

Graphical presentation of the 8-point SMPG profiles showed a comparably marked decrease in overall plasma glucose levels at endpoint (Month 6) compared with baseline in both treatment groups. The LS mean change in 24-hour average 8-point SMPG from baseline to endpoint (Month 6) was -0.78 mmol/L in the HOE901-U300 group and -1.03 mmol/L in the Lantus group. The LS mean difference between the treatment groups was 0.26 mmol/L (95% CI [-0.242 to 0.753]).

At endpoint (Month 6), the mean total daily basal insulin dose was 24.20 U (0.35 U/kg) in the HOE901-U300 group and 20.20 U (0.30 U/kg) in the Lantus group. The increase of the daily basal insulin dose was higher in the HOE901-U300 group than in the Lantus group (HOE901-U300: 8.18 U [0.12 U/kg]; Lantus: 4.46 U (0.06 U/kg).

Exploratory efficacy endpoints:

For the exploratory efficacy endpoint of target FPG at Month 6, the percentage of patients who reached target FPG <5.6 mmol/L (100 mg/dL) at Month 6 was numerically lower in the HOE901-U300 group (33.9%) than the Lantus group (40.3%). 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 treatment period was also numerically lower in the HOE901-U300 group (28.8%) than in the Lantus group (34.5%). The percentage of patients who reached target FPG <6.7 mmol/L (120 mg/dL) with no severe and/or confirmed (<3.0 mmol/L [54 mg/dL]) hypoglycemia during the last 3 months of the main 6-month treatment period was numerically higher in the HOE901-U300 group (58.5%) than in the Lantus group (55.5%).

The mean of average pre-breakfast SMPG at baseline was comparable in the HOE901-U300 group (7.68 mmol/L) and in the Lantus group (7.29 mmol/L). During the first 2 weeks of treatment, a slight increase was observed in the HOE901-U300 group versus a decrease in the Lantus group. At Month 6, a similar average pre-breakfast SMPG was reached in both treatment groups (last observation carried forward [LOCF] mean: HOE901-U300: 6.50 mmol/L; Lantus: 6.23 mmol/L).

Results of the analyses based on 7-point SMPG profiles per time point were overall consistent with those based on 8-point SMPG profiles at baseline and endpoint (Month 6). Results of the analyses on mean of pre-prandial values based on 4-point SMPG profiles were generally consistent with those based on 8-point SMPG profiles.

The LS mean change from baseline to Month 6 in plasma concentration of FFA was almost similar in both treatment groups.

Two patients (1.7%) in the HOE901-U300 group and none in the Lantus group received rescue therapy.

Other: 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.

CGM endpoint:

Mean AUC_{mean_24h} (2^{nd} day of CGM) at Month 6 was slightly lower compared to baseline in both treatment groups with a point estimate of the treatment ratio of 1.00 (95% CI: 0.73 to 1.39).

The mean CGM profile at Month 6 suggests smaller glucose excursions over time in the HOE901-U300 group and the Lantus group compared to baseline including during the nocturnal period.

Mean AUC_{mean_noc} (2^{nd} 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 0.74 (95% CI: 0.41 to 1.32).

Mean duration of TBG (80 to 140 mg/dL) on the 2^{nd} day of CGM terms at Month 6 was longer compared to baseline in both treatment groups.

Safety results:

Overall, hypoglycemia was reported by a consistently lower percentage of patients in the HOE901-U300 group than in the Lantus group (70.8% [85/120]) versus 80.0% [96/120]). This difference was also observed for events of nocturnal hypoglycemia (HOE901-U300: 30.8% [37/120]; Lantus: 47.5% [57/120]). During the first 8 weeks of study treatment, a lower percentage of patients experienced hypoglycemia in the HOE901-U300 group (42.5%) compared to the Lantus group (59.2%). During the main 6-month on-treatment period, severe hypoglycemia was reported in 3/120 (2.5%) HOE901-U300 patients and 2/120 (1.7%) Lantus patients. Severe nocturnal hypoglycemia was reported by 1/120 (0.8%) patients in the HOE901-U300 group and 2/120 (1.7%) patients in the Lantus group. Severe and/or confirmed hypoglycemia by SMPG ≤3.9 mmol/L (70 mg/dL) was reported by numerically lower percentages of patients in the HOE901-U300 group (65.0% [78/120]) than in the Lantus group (76.7% [92/120]).

The percentages of patients with any TEAEs (HOE901-U300: 70/120 [58.3%]; Lantus: 68/120 [56.7%]) were similar between two treatment groups. A similar proportion of patients experienced serious TEAEs in both treatment groups (HOE901-U300: 5/120 [4.2%]; Lantus: 4/120 [3.3%]).

No deaths were observed during the main 6-month on-treatment period in both treatment groups.

A similar number of patients in both treatment groups experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300: 3/120 [2.5%]; Lantus: 1/120 [0.8%]).

No patients had ALT >10 × the upper limit of normal (ULN) during the main 6-month on-treatment period; no patients in the HOE901-U300 group and 1 patient in the Lantus group had ALT >3 × ULN.

No symptomatic overdose with IMP/NIMP was reported during the 6-month on-treatment period in either treatment group. Asymptomatic overdose with IMP was reported by 1 patient in the HOE901-U300 group.

No 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 similar percentage of patients in both treatment groups (HOE901-U300: 11/120 [9.2%]; Lantus: 10/120 [8.3%]).

Overall injection site reactions during the main 6-month on-treatment period were reported by a similar and low percentage of patients in both treatment groups (HOE901-U300: 2/120 [1.7%]; Lantus: 1/120 [0.8%]).

After the 6-month treatment, the mean body weight reduced in the HOE901-U300 group (-0.61 kg) and increased slightly in the Lantus group (0.34 kg). The LS mean difference of the change in body weight between the treatment groups was -1.00 (95% CI [-1.528 to -0.467]).

No major differences over time or between treatment groups were observed for AIA status and AIA titer. Among patients positive for AIA, the percentage of those with antibodies cross-reacting with human insulin was slightly lower in the HOE901-U300 group than in the Lantus group. In AIA-positive patients, the decrease in HbA_{1c} was smaller in the HOE901-U300 group than in the Lantus group, which was accompanied by a smaller change in basal insulin dose in the HOE901-U300 group compared to the Lantus group. There was no major difference concerning the effect of AIA on safety endpoints.
Issue date: 18-Feb-2015

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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: NCT01689142, UTN U1111-1130-3649 Study code: EFC12512
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® Both in Combination with Oral Antihyperglycemic Drug(s) in Japanese Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period (EFC12512 - 12-months)	
Study center(s): 31 centers in Japan	
Study period: Date first patient enrolled: 21/Sep/2012 Date last patient completed: 02/Jun/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 are 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.

Primary objective: To compare the efficacy of HOE901-U300 and Lantus in terms of change in glycosylated hemoglobin (HbA_{1c}) from baseline to endpoint (scheduled at Month 6 [Week 26]) in patients with type 2 diabetes mellitus (T2DM).

Secondary objectives:

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

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), are reported in an earlier CSR.

Number of patients:	Planned: 240 (120 per treatment arm) Randomized: 241 (HOE901-U300: 121; Lantus: 120) Treated: 240
Evaluated:	
	Efficacy: 240
	Safety: 240

Diagnosis and criteria for inclusion: Inclusion criteria: Patients with T2DM; signed written informed consent. Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10.0% at screening; diabetes other than T2DM; less than 6 months on basal plus oral antihyperglycemic drug(s) (OADs) and SMPG; use of premix insulin or insulin detemir at 2 times or more a day or glucagon-like peptide 1 receptor agonists in the last 3 months, or an insulin pump within the last 6 months; use of mealtime insulin (rapid-acting insulin analog and short-acting insulin) for more than 10 days in the last 3 months before screening visit; severe hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months before screening visit.

Study treatments

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

Formulations: 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 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 5.6 mmol/L (80 to 100 mg/dL). Best efforts were made to reach the target range by 8 to 12 weeks pos-trandomization; glycemic targets could be adapted for individual patients, if deemed necessary:

- By +1.5 U for HOE901-U300 or +1 U for Lantus; if the median fasting of SMPG of last 3 days was in the range of >5.6 mmol/L and <7.8 mmol/L (>100 mg/dL and <140 mg/dL)
- By +3 U for HOE901-U300 or +2 U for Lantus, if the median fasting SMPG of last 3 days was ≥7.8 mmol/L (≥140 mg/dL)
- By -3 U for both HOE901-U300 and Lantus, if the median fasting SMPG of last 3 days was in the range of ≥3.3 mmol/L and <4.4 mmol/L (≥60 mg/dL and <80 mg.dL)
- By -3 U for both HOE901-U300 and Lantus or at the discretion of the Investigator, if the median of fasting SMPG of the last 3 days was <3.3 mmol/L (<60 mg/dL) or occurrence of >2 symptomatic or 1 severe hypoglycemia episode in the preceding week.

Non-investigational medicinal products: Mandatory background therapy (OADs)

Patients in both treatment groups were to continue with OADs during the study as received prior to the study. In the case of 2 or more symptomatic or 1 severe hypoglycemic episode, it was recommended to reduce the dose of sulfonylurea or glinide in patients treated with sulfonylurea or glinide. For patients treated with other OAD(s), the dose was reduced based on the Investigator's best medical judgment.

Rescue treatment

After the titration period (ie, after Week 12), if the basal insulin dose adjustment and appropriate other actions failed to decrease FPG/HbA_{1c} under the threshold values of 11 mmol/L (200 mg/dL) for FPG and 8.5% for HbA_{1c} and no apparent reason for insufficient control was identified, intensification of the treatment was to be considered. The choice of the antidiabetic treatment to be added to the basal insulin and oral antihyperglycemia background therapy was based on the Investigator's decision and local labeling documents.

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 post-treatment 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: SMPG (including pre-injection SMPG, variability of pre-injection SMPG, variability of 7-point SMPG profiles, fasting [pre-breakfast] SMPG, and 4-point SMPG profiles), FPG, daily average basal insulin dose, and other laboratory endpoints (C-peptide and free fatty acids [FFA]).

Efficacy evaluated for the 4-week follow-up period included observed values and change from 4-week follow-up baseline (Month 12/end of treatment) to Month 13 in average fasting (pre-breakfast) SMPG, 4-point SMPG profiles, and daily average basal insulin doses.

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, increased alanine aminotransferase [ALT], pregnancy, symptomatic overdose with IMP/non-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), Month 6 (Visit 14), and Month 12 (Visit 18). 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; an analysis of covariance/analysis of variance (ANCOVA/ANOVA) approach using a last observation carried forward (LOCF) procedure was used to analyze change from baseline. The same methodology was used to analyze change from baseline to Month 12 on key efficacy variables, ie, HbA_{1c}, FPG, pre-injection SMPG (average and variability), and 24-hour 7-point SMPG profile (average and variability).

The efficacy analyses were also conducted on the 4-week follow-up population during the 4- week follow-up period for average fasting (pre-breakfast) SMPG, 4-point SMPG profiles, and daily average basal insulin dose.

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 post-treatment period for both the safety and 4-week follow-up populations. Unless otherwise specified, the analysis of the safety variables was 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 241 patients with T2DM were randomized to HOE901-U300 (121 patients) or to Lantus (120 patients); 240/241 were exposed to IMP (safety population). The mITT population (efficacy population) included 240 patients.

Overall, a higher percentage of patients discontinued the study in the HOE901-U300 group (13/121, 10.7%) compared with the Lantus group (5/120, 4.2%).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 60.8 years; 102/241 patients (42.3%) were ≥65 years. One hundred forty-seven (147)/241 (61.0%) of the patients were male. All patients were Asian/Oriental. The mean body mass index at baseline was 25.3 kg/m^2. The mean duration of T2DM prior to study start was 14.0 years, the mean duration of prior treatment with basal insulin was 2.45 years and the median daily basal insulin dose was 0.218 U/kg body weight. Mean HbA_{1c} at baseline was 8.02%.

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 largest decrease occurred during the first 12 weeks of treatment. Mean HbA_{1c} levels at Month 12 were similar in both treatment groups. Mean change from baseline to Month 12 was also similar in both treatment groups (mean change from baseline to Month 12: -0.28% in the HOE901-U300 group and -0.33% in the Lantus group). During the 6-month safety extension period, HbA_{1c} remained stable, although HbA_{1c} tended to increase again, more in the Lantus group than in the HOE901-U300 group.

Similar to the results for HbA_{1c}, FPG decreased in both treatment groups during the 12-month on-treatment period, primarily during the initial 12 weeks of study treatment and remained stable during the 6-month safety extension period in both treatment groups. The other parameters of glycemic control, such as pre-injection SMPG (using Day 1 as baseline) and 24-hour average plasma glucose, decreased from baseline to Month 12 endpoint in both treatment groups.

Mean 7-point SMPG profiles decreased from baseline to Month 12 in both treatment groups at all time points. At Month 12, mean plasma glucose levels were comparable in both treatment groups at time points between prelunch and bedtime, whereas at pre-breakfast and postbreakfast, mean plasma glucose levels were higher in the HOE901-U300 group than in the Lantus group.

These changes in glycemic control were observed while the basal insulin doses in both treatment groups were increased, mostly during the first 12 weeks and to a greater extent in the HOE901-U300 group. Mean daily basal insulin dose was maintained from Week 12 to Month 12, with minor increases in both treatment groups. The basal insulin dose was higher in the HOE901-U300 group (25.08 U [0.36 U/kg]) compared with the Lantus group (20.63 U [0.30 U/kg]).

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

Safety results:

During the 12-month on-treatment period, the percentage of patients with at least 1 hypoglycemia event of any category at any time of the day was comparable between the HOE901-U300 and Lantus groups (98/120 patients [81.7%] in the HOE901-U300 group versus 101/120 patients [84.2%] in the Lantus group). The percentage of patients with at least one nocturnal hypoglycemia event (any category) was lower in the HOE901-U300 group than the Lantus group (50/120 patients [41.7%] versus 65/120 patients [54.2%], respectively). A similar percentage of patients reported at least 1 severe hypoglycemia in the HOE901-U300 group (3 events in 3 patients) and the Lantus group (2 events in 2 patients). The percentage of patients reporting nocturnal severe hypoglycemia was the same in both treatment groups (1 event in 1 patient in each treatment group).

No patients died during the study.

The percentage of patients with any TEAEs (94/120 patients [78.3%] in the HOE901-U300 group and 88/120 patients [73.3%] in the Lantus group) or with serious TEAEs (12/120 patients [10.0%] in the HOE901-U300 group and 8/120 patients [6.7%] in the Lantus group) were similar between both treatment groups.

A similar number of patients in both treatment groups experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300: 4/120 patients [3.3%]; Lantus: 2/120 patients [1.7%]). Two patients in the Lantus group (versus no patients in the HOE901-U300 group) experienced a confirmed major adverse cardiovascular event (cerebral infarction). Injection site reactions (HOE901-U300: 1.7%; Lantus: 0.8%) and hypersensitivity reactions (HOE901-U300: 13.3%; Lantus: 11.7%) were reported by a similar percentage of patients in the HOE901-U300 and Lantus groups during the 12-month on-treatment period.

There were no major differences in the immunogenicity profiles between the HOE901-U300 and Lantus treatment groups. The changes in daily basal insulin doses were larger in the HOE901-U300 group compared to the Lantus group in AIA-negative patients, whereas this difference between treatment groups was not apparent in AIA-positive patients. There was no obvious difference concerning the effect of AIA on 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:

At the end of the 12-month on-treatment period with HOE901-U300 or Lantus, patients were switched from IMP (HOE901-U300 or Lantus) to a commercial basal insulin regimen (Lantus in ≥92.1% of patients). A total of 226/241 (93.8%) randomized patients (post HOE901-U300: 112/121 [92.6%]; post Lantus: 114/120 [95.0%]) participated in the 4-week follow-up period.

During the first week of the 4-week follow-up period, the decrease in basal insulin dose was larger in patients in the post-HOE901-U300 group (-1.38 U) than in patients in the post Lantus group (-0.46 U). Thereafter, basal insulin dose levels remained almost unchanged up to the end of the 4-week follow-up period.

Following the switch to commercial basal insulin (primarily Lantus), hypoglycemia was reported in a higher percentage of patients in the post-HOE901-U300 group (65/112 patients [58.0%]) vs. the post-Lantus group (47/114 patients [41.2%]). Although most hypoglycemia events were reported during the daytime between 06:00 and 23:59 hours, the increase in events was particularly marked for nocturnal hypoglycemia (post-HOE901-U300: 18/112 patients [16.1%]; post-Lantus: 11/114 patients [9.6%]). No severe hypoglycemia was reported during the 4-week follow-up period.

Reports of post-treatment 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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