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	**Study Identifiers:** NCT01499082, EudraCT 2010-023769-23
Drug substance(s): HOE901-U300 (insulin glargine)	**Study code:** EFC11628

Title of the study: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period (EFC11628-6-months)

Study center(s): Multicenter (181 centers in 13 countries)

Study period:

Date first patient enrolled: 15/Dec/2011

Date last patient completed: 30/Jan/2013

Phase of development: Phase 3

Objectives:

Primary objective: To assess the effects on glycemic control of HOE901-U300 in comparison to Lantus when given as basal insulin in a regimen with mealtime insulin in terms of change in hemoglobin A_{1c} (HbA_{1c}) over a period of 6 months in patients with type 2 diabetes mellitus (T2DM).

Main secondary objective:

- To compare HOE901-U300 and Lantus in terms of occurrence of nocturnal hypoglycemia, change in pre-injection plasma glucose, and change in variability of pre-injection plasma glucose.

Further secondary objectives:

- To compare HOE901-U300 and Lantus in terms of reaching target HbA_{1c} values and controlled plasma glucose;
- To compare HOE901-U300 and Lantus in terms of treatment satisfaction of patients using the Diabetes Treatment Satisfaction Questionnaire (status; DTSQs);
- To assess the safety and tolerability (including development of anti-insulin antibodies [AIA]) of HOE901-U300.

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 (400 with HOE901-U300 and 400 with Lantus) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to Month 6) as well as to allow conclusions on the first main secondary endpoint (occurrence of nocturnal hypoglycemia).

Number of patients:	Planned: 800 (400 per treatment arm)	Randomized: 807
	Treated: 807	
Evaluated:	Efficacy: 804	Safety: 806

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with T2DM as defined by the World Health Organization; signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; less than 1 year on basal plus mealtime insulin and self-monitoring of blood glucose; use of premix insulins or basal insulins other than insulin glargine or neutral protamine hagedorn (NPH) and/or use of any non-insulin antihyperglycemic drugs other than metformin in the last 3 months before screening; total daily dose insulin glargine <42 U or equivalent dose of NPH in the last 4 weeks prior to the study (if NPH was used as basal insulin prior to the study).

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 (prefilled; ie, disposable pen). 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 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 NPH once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to the median of the total daily basal insulin doses in the last 3 days prior to the baseline visit.

Patients on NPH more than once daily prior to the baseline visit: the daily dose of HOE901-U300 or Lantus (U) was to be approximately 20% less than the median of the total daily NPH insulin doses in the 3 days prior to the baseline visit.

The basal insulin dose was adjusted once weekly to achieve fasting self-measured plasma glucose (SMPG) in the target range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL):

- by +3 U, 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 +6 U, if the median fasting SMPG of last 3 days was ≥7.8 mmol/L (≥140 mg/dL)
- by -3 U, 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).

Noninvestigational medicinal products: mandatory background therapy (short-acting mealtime insulin analog and if taken before study start, metformin).

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 as basal insulin doses were increased.

Patients in both treatment groups were to continue with their mealtime insulin analog during the study. Patients on concomitant metformin treatment were to continue during the study on a stable dose as received prior to the study, unless safety concerns necessitated a dose reduction or discontinuation of metformin.

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).

Criteria for evaluation:

Efficacy:

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

Main secondary efficacy endpoints: incidence of patients (%) with at least one nocturnal hypoglycemia between start of Week 9 and endpoint (Month 6), indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL); change in pre-injection SMPG from baseline to endpoint (Month 6) and change in variability of pre-injection SMPG from baseline to endpoint (Month 6).

Other secondary efficacy endpoints included proportion (%) of patients with HbA_{1c} <7%, change in fasting plasma glucose (FPG), change in 8-point SMPG profiles, change in total insulin dose. Treatment satisfaction was assessed using the DTSQs.

Safety: Hypoglycemia, occurrence of adverse events particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), injection site reactions and hypersensitivity reactions, physical examination, other safety information including clinical laboratory data, vital signs (including body weight), 12-lead electrocardiogram (ECG) and AIA.

Anti-insulin antibody sampling times and bioanalytical methods:

Samples for AIA assessment were to be collected at baseline (Visit 3), 4 weeks (Visit 6), 3 months (Visit 8), 6 months (Visit 10), and 12 months (Visit 12) and in case of premature discontinuation from the study treatment. Anti-insulin antibodies were determined at a central laboratory using a validated AIA binding assay methodology.

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%), and country 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 (CI) 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 modified intent-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.

Only if noninferiority of HOE901-U300 versus Lantus had been demonstrated for the primary endpoint, would testing for superiority of HOE901-U300 over Lantus on the main secondary endpoints occur within the frame of a hierarchical testing procedure. Safety analyses were descriptive, based on the safety population

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

Population characteristics:

A total of 807 patients with T2DM were randomized to HOE901-U300 (404 patients) or to Lantus (403 patients); 806 patients were exposed to the investigational medicinal product (IMP; safety population). The mITT population (efficacy population) included 804 patients.

Overall, a comparable number of patients in each treatment group discontinued the study prematurely (HOE901-U300: 30/404, 7.4%; Lantus 31/403, 7.7%).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 60 years; 246/807 (30.5%) patients were ≥65 years, and 427/807 (52.9%) of the patients were male. The majority of patients were Caucasian (745/807; 92.3%).The mean body mass index (BMI) at baseline was 36.6 kg/m², 86.6% of patients had a BMI ≥30 kg/m². The mean duration of diabetes prior to study start was 15.8 years, the mean duration of prior treatment with basal insulin was 6.6 years and the median total daily insulin dose was 1.1 U/kg body weight. Mean HbA_{1c} at baseline was 8.15%.

Research activities were terminated at 1 site (7 patients randomized) due to noncompliance with the clinical protocol and violations of good clinical practice. This noncompliance had no impact on the primary efficacy results.

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 (-0.83% [95% CI: -0.946 to -0.709] on HOE901-U300 and -0.83% [95% CI: -0.944 to -0.706] on Lantus). Noninferiority of HOE901-U300 versus Lantus was demonstrated with the LS mean difference in HbA_{1c} versus Lantus of -0.00% (95% CI: -0.112 to 0.107) and an upper bound 95% CI lower than the predefined noninferiority margin of 0.4%, and an observed value of <0.3%. Superiority of HOE901-U300 versus Lantus was not demonstrated.

First main secondary efficacy endpoint: The incidence of patients with at least one nocturnal severe and/or confirmed hypoglycemia between start of Week 9 and Month 6 was lower in the HOE901-U300 group (146 of 404 patients [36.1%]) than in the Lantus group (184 of 400 patients [46.0%]). Superiority of HOE901-U300 versus Lantus was shown with a relative risk of 0.79 ([95% CI: 0.67 to 0.93]; p = 0.0045).

Second main secondary efficacy endpoint: The LS mean change in pre-injection SMPG from baseline to endpoint (Month 6) was similar in the HOE901-U300 (-0.90 mmol/L [-16.25 mg/dL]) and Lantus groups (-0.84 mmol/L [-15.09 mg/dL]). The difference between the treatment groups was not statistically significant (LS mean difference of -0.06 mmol/L [95% CI: -0.383 to 0.254]; -1.16 mg/dL [95% CI: -6.895 to 4.571]; p = 0.6909).

Third main secondary efficacy endpoint: As the superiority of HOE901-U300 versus Lantus was not demonstrated for the second main secondary endpoint, no further test was performed for the third main secondary endpoint (change in variability of pre-injection SMPG at Month 6). The LS mean change in variability of pre-injection SMPG from baseline to Month 6 was similar in the HOE901-U300 (-1.10 [95% CI: -3.502 to 1.295]) and Lantus groups (-1.08 [95% CI: -3.476 to 1.324]).

Other secondary efficacy endpoints (Month 6):

A similar proportion of patients reached HbA_{1c} <7% in both treatment groups. Mean change in FPG, average 24-hour plasma glucose and self-monitored fasting plasma glucose were similar between treatment groups. Graphical presentation of the 8-point SMPG profiles of HOE901-U300- and Lantus-treated patients showed almost superimposable profiles with a marked decrease in plasma glucose at all timepoints compared with baseline.

At the end of the 6-month treatment period, the mean basal insulin dose was higher in the HOE901-U300 group (103 U; 0.97 U/kg) than in the Lantus group (94 U; 0.88 U/kg). Mealtime insulin doses were similar in both treatment groups (0.55 U/kg; total daily insulin dose HOE901-U300: 1.53 U/kg, Lantus 1.43 U/kg).

The overall treatment satisfaction of the patients in both treatment groups measured by DTSQs was good and similar throughout the study. More than half of the patients in each group experienced an improvement in satisfaction.

Safety results:

Overall, hypoglycemia was reported by a lower or similar percentage of patients in the HOE901-U300 group than in the Lantus group. This difference in favor of HOE901-U300 was even more evident for events of nocturnal hypoglycemia and for the first 2 months of study treatment. Analyses of hypoglycemia event rate per patient-year exposure yielded similar results to those observed for percentages of patients with hypoglycemia. During the main 6-month on-treatment period severe hypoglycemia was reported in 20/404 (5.0%) HOE901-U300-treated patients and 23/402 (5.7%) Lantus-treated patients.

The percentages of patients with any TEAEs (228/404 patients [56.4%] on HOE901-U300 and 218/402 patients [54.2%] on Lantus) or with serious TEAEs (26 patients [6.4%] on HOE901-U300 and 21 patients [5.2%] on Lantus) were similar between both groups.

A similar proportion of patients experienced serious cardiac TEAEs (System Organ Class Cardiac disorders) in both treatment groups (6 patients [1.5%] on HOE901-U300 and 7 patients [1.7%] on Lantus).

During the 6-month study period, 3 patients had TEAEs with fatal outcome: one patient in the HOE901-U300 group (bronchogenic carcinoma) and 2 patients in the Lantus group (recurrent depression and intoxication with diazepams; multiple conditions contributing to the fatal outcome including worsening of chronic heart failure (New York Heart Association Class IV), chronic kidney failure stage 4 with acute decompensation, decompensated diabetes, and diabetic nephropathy). Two HOE901-U300 treated patients had AEs with fatal outcome reported after discontinuation of study medication. One Lantus patient had a TEAE with fatal outcome during the safety extension period. None of the 6 deaths were considered related to study drug.

A similar number of patients in both treatment groups experienced TEAEs leading to permanent treatment discontinuation (6 patients [1.5%] on HOE901-U300 and 7 patients [1.7%] on Lantus).

Hypersensitivity reactions were reported in 19 (4.7%) patients in the HOE901-U300 group and 14 (3.5%) patients in the Lantus group, and injection site reactions in 9 patients (2.2%) and 6 patients (1.5%), respectively.

Laboratory parameter and vital sign data as well as the assessment of ECG readings did not reveal any specific safety concerns during the main 6-month on-treatment period. The effect on body weight was neutral in both treatment groups.

There was no difference between treatment groups in terms of the incidence of patients with AIA, AIA titer, and cross-reactivity to human insulin, nor was there any difference concerning the effect of AIA on efficacy and safety endpoints.
Issue date: 15-Oct-2015

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Sponsor / Company: Sanofi Drug substance(s): HOE901-U300 (insulin glargine)	Study Identifiers: NCT01499082, EudraCT 2010-023769-23 Study code: EFC11628
Title of the study: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period Administration Substudy Comparing Adaptable Dosing Intervals with Fixed Dosing Intervals	
Study center(s): Multinational, multicenter (62 centers in 11 countries)	
Study period: Date first patient enrolled: 22/Oct/2012 Date last patient completed: 26/Apr/2013	
Phase of development: Phase 3	
Objectives: Primary objective: To compare the efficacy of HOE901-U300 injected once daily every 24 hours and HOE901-U300 injected once daily at intervals of 24 ±3 hours in terms of change of hemoglobin A_{1c} (HbA_{1c}) from Month 6 (main study endpoint = baseline of 3-month administration substudy) to Month 9 (main study extension period = endpoint of 3-month administration substudy) in patients with type 2 diabetes mellitus (T2DM). Main secondary safety objective: To compare the safety of the 2 injection regimens for HOE901-U300 in terms of occurrence of hypoglycemia.	
Methodology: Patients randomized to HOE901-U300 and having received HOE901-U300 in the main 6-month on-treatment period were randomized 1:1 to administer HOE901-U300 once daily either every 24 hours (fixed dosing intervals) or every 24 ±3 hours (adaptable dosing intervals). Patients on HOE901-U300 completing the main 6-month on-treatment period and meeting the eligibility criteria for the 3-month administration substudy were eligible for the substudy. No specific sample size was determined for this exploratory study.	
Number of patients:	Planned: Up to 300 (150 per treatment arm) Randomized: 109 (56 to adaptable dosing intervals arm, 53 to fixed dosing intervals arm) Treated: 109
Evaluated:	Efficacy: 108 (of which 106 were evaluable) Safety: 109
Diagnosis and criteria for inclusion: Inclusion criteria: Completion of the main 6-month on-treatment period (Visit 10); randomized and treated with HOE901-U300 during the main 6-month on-treatment period (Baseline to Month 6); and signed written informed consent for the 3-month administration substudy obtained. Key exclusion criteria: Patient not willing to use the adaptable injection intervals of 24 ±3 hours on at least 2 days per week; in the Investigator's opinion, not able to comply with an adaptable dosing intervals schedule; and health condition which precludes further participation of the patient in the study.	

Study treatments

Investigational medicinal product: HOE901-U300

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) was provided in a disposable (prefilled) insulin pen.

Route(s) of administration: subcutaneous injection

Tested regimen:

Adaptable dosing intervals: HOE901-U300 administered once daily in the evening every 24 ±3 hours.

The injection time may have been adapted according to individual needs by up to 3 hours earlier or later than the daily injection time in the evening fixed at the start of the main study. The maximum intervals, ie, 3 hours earlier or 3 hours later than the fixed daily injection time were to be used on at least 2 days of the week at the patients' choice. The injection time fixed at start of the main study was to be maintained as reference time for the variation.

Control regimen:

Fixed dosing intervals: HOE901-U300, once daily injection in the evening every 24 hours.

Patients continued to inject HOE901-U300 once daily every 24 hours at the injection time fixed at start of the main study.

Dose:

The dose of HOE901-U300 was to be titrated as needed to achieve or maintain fasting plasma glucose (FPG) in the target range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL) without hypoglycemia. Changes in the insulin dose were based on fasting self-measured plasma glucose (SMPG) measurements.

Noninvestigational medicinal product(s): Patients in both treatment groups were to continue with their mealtime insulin analog during the 3-month administration substudy.

Patients on concomitant metformin treatment were to continue during the 3-month administration substudy on a stable dose, unless there was a specific safety issue related to the treatment.

Duration of treatment: The 3-month administration substudy (3-month comparative regimen period) consisted of a 3-month comparative efficacy and safety period starting at Month 6 (Visit 10) of the main study and ended at Month 9 (Visit 11) of the main study.

After completion of the 3-month administration substudy (Month 9 of main study), patients on HOE901-U300 adaptable dosing intervals regimen could continue using adaptable dosing intervals until the end of the study at Month 12 or revert to the fixed dosing intervals regimen as during the main 6-month on-treatment period. After completion of the 3-month administration substudy, patients on HOE901-U300 fixed dosing intervals regimen were to continue with this regimen up to the end of the main study.

Duration of observation: The analysis period for efficacy and safety was the 3-month administration substudy period starting at Month 6 of the main study and ending at Month 9 of the main study.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: change in HbA_{1c} from baseline (Month 6) to endpoint (Month 9).

Secondary efficacy endpoints: Change in pre-injection SMPG from baseline (Month 6) to endpoint (Month 9), change in variability of pre-injection SMPG from baseline (Month 6) to endpoint (Month 9), change in FPG from baseline (Month 6) to endpoint (Month 9), change in 8-point SMPG from baseline (Month 6) to endpoint (Month 9), change in daily basal insulin dose and total daily insulin dose (basal plus mealtime insulin) from baseline (Month 6) to endpoint (Month 9).

Safety: Hypoglycemia; occurrence of adverse events (AEs), particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); injection site reactions and hypersensitivity reactions; other safety information including vital signs and overdose.

Statistical methods: For this 3-month administration substudy, baseline was defined as Month 6 of the main study period; the endpoint was Month 9 of the main study.

The primary efficacy endpoint (change in HbA_{1c} from baseline [Month 6] to endpoint [Month 9]) was analyzed using an analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and using the HbA_{1c} baseline value as a covariate. Differences between HOE901-U300 adaptable dosing intervals regimen and HOE901-U300 fixed dosing intervals regimen and 2-sided 95% confidence intervals were estimated within the framework of ANCOVA. To assess the impact of country in the model, a sensitivity analysis excluding the country from the fixed effects of the ANCOVA model was performed.

All continuous secondary efficacy variables (except for change in variability of pre-injection SMPG) were analyzed using an ANCOVA model with treatment regimen and country as fixed effects and using the corresponding baseline value as a covariate.

Change in variability of pre-injection SMPG from baseline (Month 6) to endpoint (Month 9) was analyzed using an analysis of variance model with treatment regimen and country as fixed effects.

Safety analyses were descriptive, based on the safety substudy population.

Summary:

Population characteristics: A total of 109 patients with T2DM were randomized to the 3-month administration substudy: 56 patients to the HOE901-U300 adaptable dosing intervals regimen and 53 patients to the HOE901-U300 fixed dosing intervals regimen; 109 patients were exposed to the study treatment (safety population). The modified intent-to-treat (mITT) substudy population (efficacy population) included 108 patients.

One patient (1/56, 1.8%) randomized to HOE901-U300 adaptable dosing intervals regimen discontinued the 3-month administration substudy prematurely and also discontinued the extension period of the main study.

Demographics and patient characteristics at baseline (Month 6) were well-balanced between both dosing regimen groups. The median age of the substudy population was 61.0 years; 74/109 (67.9%) patients were <65 years, and 49/109 (45.0%) of the patients were male.

Based on the documented injection times during the weeks before Month 7.5 and Month 9, in the adaptable dosing intervals group compared to the fixed dosing intervals group there was a larger percentage of injections by patient done in the extreme long (>26.5 hours) and short intervals (<21.5 hours) as well as in the intermediate intervals (21.5 to 23 hours and 25 to 26.5 hours), and a smaller percentage of injections in the range of 23 to 25 hours. This suggests substantial variations of injection intervals in the adaptable dosing interval group. In the HOE901-U300 adaptable dosing intervals group, 30.9% of patients had ≥4 injection intervals at the extreme intervals of <21.5 or >26.5 hours and 52.7% of patients had ≥4 injection intervals of >25 or <23 hours after previous injection. In the HOE901-U300 fixed dosing intervals group, 66.7% of patients had all consecutive injection intervals within 23 to 25 hours; therefore, these patients were considered compliant with the HOE901-U300 fixed dosing intervals regimen.

Concerning the time interval between actual injection time and reference injection time (as scheduled at the main study baseline), deviations of more than 3 hours from the fixed reference injection time were seen only for few injections, suggesting that patients of both dosing interval regimen groups continued to do their injections around the fixed reference time in the evening.

Efficacy results:

Primary endpoint: The least square (LS) mean change in HbA_{1c} from baseline (Month 6) to endpoint (Month 9) was similar in the HOE901-U300 adaptable dosing intervals group (0.21% [95% CI: -0.011 to 0.429]) and HOE901-U300 fixed dosing intervals group (0.15% [95 %CI: -0.084 to 0.394]) with the LS mean difference of 0.05% [95 % CI: -0.189 to 0.298].

Secondary efficacy endpoints:

- Change in pre-injection SMPG: The LS mean change from baseline (Month 6) to endpoint (Month 9) was small and similar in both groups (HOE901-U300 adaptable dosing intervals group 0.06 mmol/L; -1.15 mg/dL; HOE901-U300 fixed dosing intervals group -0.45 mmol/L; -8;14 mg/dL, with an LS mean difference between the 2 dosing interval regimens of 0.39 mmol/L [95% CI: -0.241 to 1.016]; 6.99 mg/dL [95% CI: -4.338 to 18.309]). The pre-injection SMPG values remained similar when the injection intervals varied by ±2.5 hours from the regular interval between 2 consecutive injections.

- Change in variability of pre-injection SMPG: There was no relevant difference between the 2 dosing interval groups for the LS mean change from baseline (Month 6) to endpoint (Month 9) in variability of pre-injection SMPG.
- Change in FPG: The mean change in FPG from baseline (Month 6) to endpoint (Month 9) was small and similar between groups (HOE901-U300 adaptable dosing intervals 1.44 mmol/L; 25.85 mg/dL; HOE901-U300 fixed dosing intervals group 1.17 mmol/L; 21.01 mg/dL, with an LS mean difference between the 2 dosing interval regimens of 0.27 mmol/L [95%CI: -0.590 to 1.128]; 4.85 mg/dL [95% CI: -10.622 to 20.314]).
- 8-point SMPG profiles: The 8-point SMPG profiles (mean at each time point) during the 3-month administration substudy period were generally similar at both baseline (Month 6) and endpoint (Month 9) between the 2 dosing interval groups.
- Only minor changes in the average daily basal insulin doses and total daily insulin doses were observed over the 3-month administration substudy period for both dosing interval regimen groups.

Safety results:

During the 3-month administration substudy, hypoglycemia events, both overall and for each category of hypoglycemia, were reported for a similar percentage of patients in the HOE901-U300 adaptable dosing intervals group and HOE901-U300 fixed dosing intervals group. The rate per patient years of exposure for any hypoglycemia event and severe and/or confirmed hypoglycemia (SMPG ≤3.9 mmol/L; 70 mg/dL) was lower in the adaptable dosing intervals group compared to the fixed dosing intervals group (severe and/or confirmed hypoglycemia [SMPG ≤3.9 mmol/L; 70 mg/dL]: adaptable dosing intervals group 13.53 events per patient-year of exposure; fixed dosing intervals group 19.92 events per patient-year of exposure).

Severe hypoglycemia was reported during the substudy period in 1 patient in the fixed dosing intervals group between 00:00 and 05:59 hours (severe nocturnal hypoglycemia).

The event rate per patient years of exposure for any hypoglycemia event and similarly for severe and/or confirmed hypoglycemia (SMPG ≤3.9 mmol/L; 70 mg/dL) reported between 00:00 and 05:59 hours was higher in the adaptable dosing intervals group compared with the fixed dosing intervals group (severe and/or confirmed hypoglycemia [SMPG ≤3.9 mmol/L; 70 mg/dL]: adaptable dosing intervals group 2.39 events per patient years of exposure; fixed dosing intervals group 1.67 events per patient-year of exposure); while more daytime hypoglycemia events were reported in the fixed dosing intervals group (18.25 events per patient-year of exposure) compared with the adaptable dosing intervals group (11.43 events per patient-year of exposure).

The percentage of patients experiencing any TEAE and any serious TEAE was similar in the HOE901-U300 adaptable dosing intervals group and in the HOE901-U300 fixed dosing intervals group (any TEAE: adaptable dosing intervals group 15/56 patients [26.8%]; fixed dosing intervals group 15/53 patients [28.3%]; any serious TEAE: adaptable dosing intervals 4/56 patients [7.1%]; HOE901-U300 fixed dosing intervals 5/53 patients [9.4%]).

No TEAEs leading to treatment discontinuation, leading to death, or linked to injection site reactions were observed in either dosing interval regimen during the 3-month administration substudy period. One patient (1.9%) in the fixed dosing interval regimen experienced the serious TEAE of hypersensitivity reaction (asthma exacerbation), which was considered not related to the investigational medicinal product (IMP). The patient continued the IMP.

Issue date: 21-May-2015

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Sponsor / Company: Sanofi Drug substance(s): HOE901-U300 (insulin glargine)	Study Identifiers: NCT01499082, EudraCT 2010-023769-23 Study code: EFC11628
Title of the study: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period (EFC11628-12-months)	
Study center(s): Multicenter (181 centers in 13 countries)	
Study period: Date first patient enrolled: 15/Dec/2011 Date last patient completed: 04/Sep/2013	
Phase of development: Phase 3	

Objectives:

Primary objective: To assess the effects on glycemic control of HOE901-U300 in comparison to Lantus when given as basal insulin in a regimen with mealtime insulin in terms of change in hemoglobin A_{1c} (HbA_{1c}) over a period of 6 months in patients with type 2 diabetes mellitus (T2DM).

Main secondary objective:

- To compare HOE901-U300 and Lantus in terms of occurrence of nocturnal hypoglycemia, change in pre-injection plasma glucose (self-monitored plasma glucose [SMPG]), and change in variability of pre-injection plasma glucose (SMPG).

Further secondary objectives:

- To compare HOE901-U300 and Lantus in terms of reaching target HbA_{1c} values and controlled plasma glucose;
- To compare HOE901-U300 and Lantus in terms of treatment satisfaction of patients using the Diabetes Treatment Satisfaction Questionnaire (status; DTSQs);
- To assess the safety and tolerability (including development of anti-insulin antibodies [AIA]) of HOE901-U300.

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 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 (400 with HOE901-U300 and 400 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 (occurrence of nocturnal hypoglycemia) for the initial 6-month on-treatment period.

Number of patients:	Planned: 800 (400 per treatment arm)
	Randomized: 807 (HOE901-U300: 404; Lantus: 403)
	Treated: 806
Evaluated:	Efficacy: 804
	Safety: 806

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with T2DM as defined by the World Health Organization; signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; diabetes other than T2DM; less than 1 year on basal plus mealtime insulin and SMPG; use of premix insulins or basal insulins other than insulin glargine or Neutral Protamine Hagedorn (NPH) and/or use of any non-insulin antihyperglycemic drugs other than metformin in the last 3 months before screening; total daily dose insulin glargine <42 U or equivalent dose of NPH in the last 4 weeks prior to the study (if NPH was used as basal insulin prior to the study).

Study treatments

Investigational medicinal product(s): Tested drug - HOE901-U300; Control drug - HOE901-U100 (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 modified SoloStar® (prefilled; ie, disposable pen). 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 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. Patients from the HOE901-U300 group who participated in the 3-month administration substudy from Months 6 to 9 were re-randomized to a fixed or adaptable dosing interval regimen (HOE901-U300 once daily at the patient's established clock time ±3 hours). Substudy patients were allowed to keep to the adaptable dosing regimen up to the end of the 12-month on-treatment period.

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

The basal insulin dose was adjusted once weekly to achieve fasting SMPG in the target range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L):

- by +3 U, 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 +6 U, if the median fasting SMPG of last 3 days was ≥7.8 mmol/L (≥140 mg/dL)
- by -3 U, 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).

Noninvestigational medicinal products: mandatory background therapy (short-acting mealtime insulin analog 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. Patients on concomitant metformin treatment were to continue during the study on a stable dose as received prior to the study, unless safety concerns necessitated a dose reduction or discontinuation of metformin.

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 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 12

Other efficacy endpoints: change from baseline to Month 12 for the following: fasting plasma glucose (FPG), SMPG (including pre-injection SMPG, variability of pre-injection SMPG, 8-point SMPG profiles, mean 24-hour plasma glucose and variability of 24-hour plasma glucose based on 8-point SMPG profiles, fasting [prebreakfast] SMPG, and mean plasma glucose based on 4-point SMPG profiles), daily average insulin doses (including basal, mealtime insulin, total and ratio of basal to total), insulin dose by visit and other laboratory endpoints (including free fatty acids and C-peptide). Assessment of treatment satisfaction using DTSQs up to Month 12.

Efficacy evaluated for the 4-week follow-up period included change from baseline and follow-up baseline (Month 12/end of treatment) to Month 13 in: daily average fasting (prebreakfast) SMPG and average SMPG values based on 4-point SMPG profiles, and daily average insulin doses (including basal, mealtime, total and ratio of basal to 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 and AIA results.

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

Anti-insulin sampling times and bioanalytical methods:

Samples for anti-insulin antibody assessment were collected at baseline (Visit 3), 4 weeks (Visit 6), 3 months (Visit 8), 6 months (Visit 10), and 12 months (Visit 12) 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 intent-to-treat (mITT) population. A mixed-effects model for repeated measures (MMRM) methodology was used to analyze change from baseline to Month 12 endpoint on key efficacy variables, ie, HbA_{1c}, FPG, pre-injection SMPG (average and variability) and 8-point SMPG profile (24-hours average and variability).

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 post-treatment 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 807 patients with T2DM were randomized to HOE901-U300 (404 patients) or to Lantus (403 patients); 806/807 were exposed to the IMP (safety population). The mITT population (efficacy population) included 804 patients.

Overall, a comparable percentage of patients in each treatment group discontinued the study prematurely (HOE901-U300: 45/404, 11.1%; Lantus 47/403, 11.7%).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 60 years; 246/807 (30.4%) patients were ≥65 years. 427/807 (52.9%) of the patients were male. The majority of patients were Caucasian (745/807; 92.3%).The mean body mass index at baseline was 36.6 kg/m². The mean duration of diabetes prior to study start was 15.8 years, the mean duration of prior treatment with basal insulin was 6.6 years and the median total daily insulin dose was 1.1 U/kg body weight. Mean HbA_{1c} at baseline was 8.15%.

Efficacy results:

Mean HbA_{1c} was similar at baseline in both HOE901-U300 and Lantus treatment groups; mean HbA_{1c} decreased from baseline to Month 12 in both treatment groups. The largest decrease occurred during the first 12 weeks of treatment. The reduction in HbA_{1c} from baseline to Month 12 in the HOE901-U300 group was greater than in the Lantus group (HOE901-U300: -0.86% [95% CI: -0.949 to -0.772] versus Lantus: -0.69% [95% CI: -0.778 to -0.600]; LS mean difference -0.17% [95% CI: -0.297 to -0.046]; MMRM). HbA_{1c} remained relatively stable in the HOE901-U300 group during the 6-month extension period, while it showed a tendency to increase in the Lantus group.

Similar to the results for HbA_{1c}, the other parameters of glycemic control, such as FPG, pre-injection SMPG, and 24-hour average plasma glucose derived from 8-point profiles decreased in both treatment groups primarily during the initial 12 weeks of study treatment. These parameters remained relatively stable during the 6-month extension period in the HOE901-U300 group, although mean reduction from baseline to Month 12 for these parameters was greater in the HOE901-U300 group than in the Lantus group. Variability of 24-hour average plasma glucose had decreased more between baseline and Month 12 in the HOE901-U300 than in the Lantus group.

Mean 8-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 03:00 hours and pre-dinner, whereas at post-dinner and bedtime, mean plasma glucose levels were lower in the HOE901-U300 group than in 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 continued to increase gradually from Week 12 to Month 12 in the HOE901-U300 group, while it remained relatively stable 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 average total insulin dose was 168.77 U [1.575 U/kg] in the HOE901-U300 group and 156.72 U [1.451 U/kg] in the Lantus group. The 7.7% higher total insulin dose in the HOE901-U300 group is driven by the differences in the basal insulin dose, which was 14.1% higher in the HOE901-U300 group (109.42 U [1.025 U/kg]) compared with the Lantus group (95.85 U [0.898 U/kg]).

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

Safety results:

During the 12-month on-treatment period the percentage of patients with at least one hypoglycemia event of any category was lower in the HOE901-U300 than in the Lantus group for both, hypoglycemia with onset at any time of day (HOE901-U300: 353/404 [87.4%]; Lantus: 370/402 [92.0%]) and for nocturnal hypoglycemia (HOE901-U300: 224/404 [55.4%]; Lantus: 266/402 [66.2%]). Severe hypoglycemia was reported in 27 patients (6.7%) in the HOE901-U300 group and 30 patients (7.5%) in the Lantus group.

A total of 9 patients died during the study, 4 (1.0%) in the HOE901-U300 group and 5 (1.2%) in the Lantus group. Two patients (0.5%) in the HOE901-U300 group and 4 patients (1.0%) had a treatment-emergent adverse event (TEAE) with fatal outcome. In 2 patients in the HOE901-U300 group and 1 patient in the Lantus group, the SAEs with fatal outcome were reported post-treatment. None of the deaths were considered related to the study drug.

The percentages of patients with any TEAEs (289 of 404 patients [71.5%] on HOE901-U300 and 278 of 402 patients [69.2%] on Lantus) or with serious TEAEs (53 patients [13.1%] on HOE901-U300 and 62 patients [15.4%] on Lantus) were similar between both groups.

A similar proportion of patients in each group experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300: 2.2%; Lantus: 3.5%). Serious cardiac TEAEs were reported by a low number of patients similarly in both treatment groups (HOE901-U300: 3.0%; Lantus: 3.7%). Injection site reactions (HOE901-U300: 3.0%; Lantus: 1.5%) and hypersensitivity reactions (HOE901-U300: 6.9%; Lantus: 5.7%) were reported at a similar rate in the HOE901-U300 and Lantus groups during the 12-month on-treatment period.

There was no difference 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:

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 ≥95% patients). A total of 67/807 (8.3%) randomized patients (post HOE901-U300: 40/404 [9.9 %]; post Lantus: 27/403 [6.7%]) participated in the 4-week follow-up period.

During the first week of the 4-week follow-up period, the percentage decreases in basal and total insulin doses were larger in patients in the post HOE901-U300 group (basal -14.76%; total -10.30%) than in patients in the post Lantus group (basal -8.86%; total -6.19%), whereas changes in mealtime insulin doses were minor in both treatment groups (post HOE901-U300 +4.78%; post Lantus +1.60%). Thereafter, basal insulin dose levels remained almost unchanged up to the end of the 4-week follow-up period.

In patients previously treated with HOE901-U300 there was a small transient decrease of fasting pre-breakfast SMPG in the first week of the follow-up period. Thereafter, up to the end of the 4-week follow-up period, in both treatment groups fasting pre-breakfast SMPG was maintained within the upper range found at the end of the 12-month on-treatment period (baseline of the 4-week follow-up period).

Following the switch to commercial basal insulin (primarily Lantus), increased hypoglycemia was reported in the post HOE901-U300 group (26/40 patients [65.0%]) versus the post Lantus group (13/27 patients [48.1%]). The hypoglycemia events were mostly reported during daytime between 06:00 and 23:59 hours, although the increase was particularly marked for nocturnal hypoglycemia (post HOE901-U300: 12/40 patients [30.0%]; post Lantus: 4/27 patients [14.8%]). 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 do not suggest a safety concern.

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