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:** NCT01499095, UTN U1111-1118-6943 & EudraCT 2010-023770-39 **Study code:** EFC11629
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 in Combination with Oral Antihyperglycemic Drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-Month Safety Extension Period (EFC11629 6-months)	
Study center(s): Multicenter (213 centers in 13 countries)	
Study period: Date first patient enrolled: 14/Dec/2011 Date last patient completed: 26/Apr/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 oral antihyperglycemic drug(s) 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 preinjection 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: 811
	Treated: 809
Evaluated:	Efficacy: 808
	Safety: 809

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with type 2 diabetes mellitus as defined by the World Health Organization diagnosed for at least 1 year at the time of the screening visit; signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; diabetes other than type 2 diabetes mellitus; less than 6 months on basal insulin treatment together with oral antihyperglycemic drug(s) and self-monitoring of blood glucose; patients using premix insulins or basal insulins other than insulin glargine or Neutral Protamine Hagedorn (NPH) in the last 3 months before screening visit and patients using sulfonylurea in the last 2 months before screening visit; total daily dose insulin glargine <42 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(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 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 last 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).

Rescue treatment:

If the basal insulin adjustment failed to decrease fasting plasma glucose (FPG)/HbA_{1c} under the threshold values of 11.1 mmol/L (200 mg/dL) for FPG and 8% for HbA_{1c} at week 12 or later 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 Investigator's decision and local labeling documents.

Noninvestigational medicinal product(s) (if applicable): Patients in both treatment groups were to continue with their oral antihyperglycemic background therapy at a stable dose during the study, except sulfonylureas which were prohibited within 2 months before the screening visit and during the study. Rescue therapy was also considered as noninvestigational medicinal product (NIMP).

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 was the main 6-month on-treatment 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 was 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).

Main secondary 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 FPG, change in 8-point SMPG profiles, change in 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, and 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% for 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 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 the 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 811 patients with type 2 diabetes were randomized to HOE901-U300 (n=404) or to Lantus (n=407); 809 patients were exposed to investigational medicinal product (IMP; safety population). The mITT population (efficacy population) included 808 patients.

Overall, a comparable number of patients in each treatment group discontinued the study treatment prematurely (HOE901-U300: 36/404, 8.9%; Lantus 38/407, 9.3%).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 58.2 years; 190/811 (23.4%) patients were ≥65 years and 372/811 (45.9%) of the patients were male. The majority of patients were Caucasian (761/811; 93.8%). The mean body mass index (BMI) at baseline was 34.8 kg/m², 75.7% of patients had a BMI ≥30 kg/m^2. There were slightly more patients with a BMI above 40 kg/m² in the HOE901-U300 group (21.5%) than in the Lantus group (16.7%). The mean duration of diabetes prior to study start was 12.6 years, the mean duration of prior treatment with basal insulin was 3.8 years. The majority of patients took insulin glargine (78.8% versus NPH 21.2%) on the 7 days before start of study treatment; more patients from the Lantus group were on insulin glargine (82.8%) compared to the HOE901-U300 group (74.9%). The median daily basal insulin dose at baseline was 0.614 U/kg body weight.

Mean HbA_{1c} at baseline was similar in both treatment groups (HOE901-U300: 8.28% and Lantus: 8.22%; for evaluable patients, ie, who had a baseline and at least one post-baseline HbA_{1c} assessment).

Efficacy results:

Primary endpoint: The LS mean change in HbA_{1c} from baseline to endpoint (Month 6) was similar in both treatment groups (HOE901-U300: -0.57% (95% CI [-0.756;-0.387]); Lantus: -0.56% (95 % CI [-0.744;-0.379]). Noninferiority of HOE901-U300 versus Lantus was demonstrated with the LS mean difference in HbA1c versus Lantus of -0.01% (95 % CI [-0.139; 0.119]) with the upper bound lower than the predefined noninferiority margin of 0.4%. The observed CI also support a noninferiority margin of 0.3%. Superiority of HOE901-U300 versus Lantus was not demonstrated.

First main secondary 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 (87/403 patients [21.6%]) than in the Lantus group (113/405 patients [27.9%]). Superiority of HOE901-U300 versus Lantus was shown with a relative risk of 0.77 ([95% CI: 0.61 to 0.99]; p=0.0380).

Second main secondary endpoint: The LS mean change in pre-injection SMPG from baseline to endpoint (Month 6) was similar in the HOE901-U300 (-0.56 mmol/L [-10.01 mg/dL]) and Lantus groups (-0.51 mmol/L [-9.22 mg/dL]). The difference between the treatment groups was not statistically significant (LS mean difference of -0.04 mmol/L [95% CI: -0.438 to 0.350]; 0.79 mg/dL [95% CI: -7.883 to 6.311]; p=0.8279).

Third main secondary 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). There was a trend for a larger decrease of variability from baseline to endpoint (Month 6) in the HOE901-U300 group than in the Lantus group, as indicated by the LS mean changes: -2.34 (95% CI: 5.142 to 0.452) and 0.53 (95% CI: -3.297 to 2.231), respectively.

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 showed in both treatment groups a comparable, marked decrease in plasma glucose at all timepoints compared with baseline.

At the end of the main 6-month on-treatment period, the mean daily insulin dose was 91 U (0.92 U/kg) in the HOE901-U300 group and 82 U (0.84 U/kg) in the Lantus group.

A similar number of patients in both treatment groups received a rescue therapy during the main 6-month on-treatment period (5.7% for HOE901-U300, 4.9% for Lantus).

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, hypoglycemia was reported by a consistently lower 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 4/403 (1%) of HOE901-U300 treated patients and 6/406 (1.5%) of Lantus-treated patients.

The percentages of patients with any TEAEs (237/403 patients [58.8%] on HOE901-U300 and 206/406 patients [50.7%] on Lantus) was higher for the patients in the HOE901-U300 treatment group than in the Lantus group, with no specific System Organ Class (SOC) contributing. Serious TEAEs were reported by 15 patients (3.7%) in both treatment groups.

The proportion of patients experiencing serious cardiac TEAEs (SOC Cardiac disorders) was higher in HOE901-U300 group than in the Lantus group (6 patients [1.5%] on HOE901-U300 and 1 patient [0.2%] on Lantus). All the patients experiencing serious cardiac TEAEs suffered from preexisting, significant event related pathology, none of the events were considered as related to the IMP or NIMP by the Investigator. Overall, the number of patients experiencing cardiac TEAEs was 10 (2.5%) in the HOE901-U300 group and 5 (1.2%) in the Lantus group.

During the 6-month study period, 3 patients had TEAEs with fatal outcome: 2 patients in the HOE901-U300 group (myocardial infarction and coronary artery disease) and 1 patient in the Lantus group (exacerbation of chronic pyelonephritis). One patient in each treatment group had a TEAE with fatal outcome during the safety extension period. None of the deaths during the main 6-month on-treatment period 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 4 patients [1.0%] on Lantus).

Hypersensitivity reactions were reported in 13 (3.2%) patients in the HOE901-U300 group and 16 (3.9%) patients in the Lantus group, and injection site reactions in 4 patients (1.0%) and 12 patients (3.0%), 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.

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Sponsor / Company: Sanofi **Drug substance(s):** HOE901-U300 (insulin glargine)	**Study Identifiers:** NCT01499095, UTN U1111-1118-6943 & EudraCT 2010-023770-39 **Study code:** EFC11629

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 in Combination with Oral Antihyperglycemic Drug(s) 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 (56 centers in 8 countries)

Study period:

Date first patient enrolled: 06/Nov/2012

Date last patient completed: 24/Jul/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: 89 (45 to adaptable injection intervals, 44 to fixed dosing intervals)
	Treated: 87
Evaluated:	Efficacy: 86 (44 in the adaptable injection interval group, 42 in the fixed dosing interval group)
	Safety: 87 (44 in the adaptable injection interval group, 43 in the fixed dosing interval group)

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); signed written informed consent for 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 schedule; health condition which precludes further participation of the patient in the study.

Study treatments

Investigational medicinal product(s): HOE901-U300

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) was supplied 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 was allowed to be 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) (if applicable): Patients were to continue their oral antihyperglycemic background therapy during participation in the substudy. Doses were to be kept stable throughout the study unless there was a specific safety issue related to these treatments. No other concomitant antidiabetic treatments were to be used in this study. Short-term use (ie, 10 days at maximum) of short-acting insulin therapy (eg, due to acute illness or surgery) was not considered as rescue therapy. Rescue medication was considered as non-investigational medicinal product.

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 the HOE901-U300 adaptable dosing interval regimen could continue using adaptable dosing intervals until the end of the study at Month 12 or revert to the fixed dosing interval regimen as during the main 6-month on-treatment period. After completion of the 3-month administration substudy, patients on the HOE901-U300 fixed dosing interval 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, change in variability of pre-injection SMPG, change in FPG, change in 8-point SMPG, and change in daily basal insulin dose 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 substudy baseline [Month 6] to substudy 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 interval regimen and HOE901-U300 fixed dosing interval regimen and 2-sided 95% confidence intervals (CIs) 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 population.

Summary:

Population characteristics:

Overall, 89 patients with T2DM were randomized to the 3-month administration substudy: 45 patients to the HOE901-U300 adaptable dosing interval regimen and 44 patients to the HOE901-U300 fixed dosing interval regimen. Of the 89 randomized substudy patients, 87 were exposed to study treatment and included in the safety substudy population, 86 were included in the mITT population and 78 completed the substudy.

Demographics and patient characteristics at baseline (Month 6) were well-balanced between both dosing regimen groups. The median age of the substudy population reported at main study baseline was 58.0 years and 49.4% of the patients were male. Three patients received insulins and analogs (started as rescue therapy during the main study): 1 patient on the HOE901-U300 adaptable dosing interval regimen received insulin glulisine, and 2 patients on the HOE901-U300 fixed dosing interval regimen received insulin aspart. No patients started rescue therapy during the 3-month administration substudy.

Based on the documented injection times during the last 7 days before Month 7.5 and Month 9, in the adaptable dosing interval group compared to the fixed dosing interval group there was a larger percentage of injections by patient administered 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. Patients randomized to the HOE901-U300 adaptable dosing interval arm mostly complied with the allocated dosing regimen. In the HOE901-U300 adaptable dosing interval group, 47.5% of patients had ≥4 injection intervals at the extreme intervals of <21.5 or >26.5 hours and 67.5% of patients had ≥4 injection intervals of >25 or <23 hours after the previous injection. In the HOE901-U300 fixed dosing interval group, 61.5% of patients had all consecutive injection intervals within 23 to 25 hours and were therefore compliant.

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 a few injections, suggesting that patients in both dosing interval regimen groups continued to administer their injections around the fixed reference time in the evening.

Efficacy results:

Primary efficacy endpoint:

The least square (LS) mean change from baseline (Month 6) to endpoint (Month 9) in HbA_{1c} was similar for both regimens: -0.12% (95% CI: -0.422 to 0.183) for the HOE901-U300 adaptable dosing interval regimen and -0.25% (95% CI: -0.574 to 0.072) for the HOE901-U300 fixed dosing interval regimen. The LS mean difference between the regimens in the mean change in HbA_{1c} from baseline (Month 6) to endpoint (Month 9) was 0.13% (95% CI: -0.152 to 0.415).

Secondary efficacy endpoint:

Change in pre-injection SMPG: The LS mean change from baseline (Month 6) to endpoint (Month 9) in average pre-injection SMPG was similar for both regimens: -1.10 mmol/L (-19.80 mg/dL) for the HOE901-U300 adaptable dosing interval regimen and -1.33 mmol/L (-23.97 mg/dL) for the HOE901-U300 fixed dosing interval regimen. The LS mean difference between the regimens was 0.23 mmol/L (95% CI: -0.576 to 1.039); 4.17 mg/dL (95% CI: -10.370 to 18.708). The LS mean change from baseline (Month 6) to endpoint (Month 9) in pre-injection SMPG by time interval (between 2 consecutive injections) was 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. The LS mean difference between the regimens was -0.21 mmol/L (95% CI: -1.200 to 0.784); -3.74 mg/dL (95% CI: -21.609 to 14.132).

Eight-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 HOE901-U300 adaptable dosing interval group and HOE901-U300 fixed dosing interval group.

Change in daily basal insulin dose: Only minor changes in the average daily basal 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 interval group and HOE901-U300 fixed dosing interval group. A total of 73 hypoglycemia events were reported in 16 patients (6.64 events per patient-year of exposure) in the adaptable dosing interval group and 96 hypoglycemia events in 18 patients (9.21 events per patient-year of exposure) in the fixed dosing interval group. The slight difference was mostly due to fewer documented symptomatic hypoglycemia events (confirmed by SMPG ≤3.9 mmol/L; 70 mg/dL) in the adaptable dosing interval group (35 events; 3.18 events per patient-year of exposure) compared with the fixed dosing interval group (53 events; 5.09 events per patient-year of exposure). The number of hypoglycemia events and events per patient-year of exposure were similar for the other individual categories. The higher number of documented symptomatic hypoglycemia events in the fixed dosing interval groups also contributed to the difference in the number of events and event rate between the 2 groups in the composite category of severe and/or confirmed hypoglycemia (SMPG ≤3.9 mmol/L; 70 mg/dL): 72 events in the adaptable dosing interval group (6.55 events per patient-year of exposure), 87 events in the fixed dosing interval group (8.35 events per patient-year of exposure). There was no event of severe hypoglycemia reported in the substudy.

The number of events and the event rate per patient-year of exposure for any hypoglycemia event reported between 00:00 and 05:59 hours was similar in the adaptable dosing interval group (24 events; 2.18 events rate per patient-year of exposure) and fixed dosing interval group (24 events; 2.30 events per patient-year of exposure). During daytime, the number of hypoglycemia events and the rate per patient-year of exposure in any hypoglycemia category and in the category of severe and/or confirmed hypoglycemia (SMPG ≤3.9 mmol/L; 70 mg/dL) were slightly lower in the adaptable dosing interval group compared to the fixed dosing interval group (any hypoglycemia event: adaptable dosing interval group: 49 events, 4.45 events per patient-year of exposure; fixed dosing interval group: 72 events, 6.91 events per patient-year of exposure. This difference between the 2 groups was mostly due to a lower number of documented symptomatic events (SMPG ≤3.9 mmol/L; 70 mg/dL) in the adaptable dosing interval group compared to the fixed dosing interval group (adaptable dosing interval group: 24 events; 2.18 events per patient-year of exposure; fixed dosing interval group: 35 events; 3.36 events per patient-year of exposure). The number of hypoglycemia events and events per patient-year of exposure was similar between the 2 dosing interval groups for the other hypoglycemia categories during daytime.

Taking into account the small denominator, the percentage of patients with TEAEs during the 3-month administration substudy was similar in the HOE901-U300 adaptable dosing interval regimen (20.5% of patients) and HOE901-U300 fixed dosing interval regimen (25.6% of patients).

Serious TEAEs (spinal osteoarthritis and chest pain) were reported in 2 patients (4.5%; both on the HOE901-U300 adaptable dosing interval regimen) during the 3-month administration substudy. The chest pain (non-cardiac) was reported in a patient with a one day history of exertional chest pain, located in the interscapular area and radiating circumferentially. An electrocardiogram showed no acute ischemic changes. No action was taken regarding the investigational medicinal product (IMP), and both TEAEs were assessed as not related to study medication. One patient on the HOE901-U300 adaptable dosing interval regimen had a mild accidental symptomatic overdose with the IMP which was not serious. No action was taken with the IMP. This event of accidental symptomatic overdose was assessed as related to study medication. No deaths were reported, and no TEAEs led to permanent treatment discontinuation during the 3-month administration substudy. In addition, no injection site reactions and no hypersensitivity reactions were reported.
Issue date: 20-May-2015

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	**Study Identifiers:** NCT01499095, UTN U1111-1118-6943, EudraCT 2010-023770-39 **Study code:** EFC11629
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 in combination with oral antihyperglycemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period	
Study center(s): Multicenter (213 centers in 13 countries)	
Study period: Date first patient enrolled: 14/Dec/2011 Date last patient completed: 22/Nov/2013	
Phase of development: Phase 3	

Objectives: The primary and secondary objectives of the study (described below) were based on the initial 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 assess the effects on glycemic control of HOE901-U300 in comparison to Lantus when given as basal insulin in a regimen with oral antihyperglycemic drug (OAD)(s) in terms of glycated hemoglobin A1c (HbA_{1c}) change over a period of 6 months in patients with type 2 diabetes mellitus (T2DM).

Main secondary objectives:

- 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.

Following Month 12, after the end of the 6-month safety extension period, patients completed a follow-up visit 2 days after completion 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 (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.

Results based on the main 6-month on-treatment period, including the primary efficacy analysis which tested the non inferiority 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. The results of patients from the HOE901-U300 group who participated in a 3-month administration substudy from Months 6 to 9 have also been reported in a separate CSR.

Number of patients**:**	Planned: 800 (400 per treatment arm)
	Randomized: 811 (HOE901-U300: 404; Lantus: 407)
	Treated: 809
Evaluated:	
	Efficacy: 808
	Safety: 809

Diagnosis and criteria for inclusion: Inclusion criteria: Patients with T2DM as defined by World Health Organization diagnosed for at least 1 year at the time of the screening visit; signed written informed consent. Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; diabetes other than T2DM; less than 6 months on basal insulin treatment together with OAD(s) and self-monitored plasma glucose (SMPG); patients using premix insulins or basal insulins other than insulin glargine or neutral protamine Hagedorn (NPH) in the last 3 months before screening visit and patients using sulfonylurea in the last 2 months before screening visit; 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 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(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. 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 of HOE901-U300 or Lantus (U) 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 last 3 days 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):

- 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).

Rescue treatment:

If the basal insulin adjustment failed to decrease fasting plasma glucose (FPG) / HbA_{1c} under the target values of 11.1 mmol/L (200 mg/dL) for FPG and 8% for HbA_{1c} at Week 12 or later 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 OAD background therapy was based on Investigator's decision and local labeling documents.

Noninvestigational medicinal product(s): Patients in both treatment groups were to continue with their OAD background therapy at a stable dose during the study, except sulfonylureas which were prohibited within 2 months before the screening visit and during the study. Rescue therapy was also considered as noninvestigational medicinal product (NIMP). Short-term use (ie, 10 days at maximum) of short-acting insulin therapy (eg, due to acute illness or surgery) was not considered as rescue therapy.

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} by visit from baseline to Month 12.

Other efficacy endpoints: change in baseline to Month 12 for the following: 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 profiles, fasting [prebreakfast] SMPG and mean of pre-prandial values based on 4-point SMPG profiles), daily basal insulin doses by visit and other laboratory endpoints (including free fatty acids [FFA] and C-peptide). Assessment of treatment satisfaction using Diabetes Treatment Satisfaction Questionnaire (DTSQs) up to Month 12.

Efficacy endpoints evaluated for the 4-week follow-up period included change from follow-up baseline (Month 12/end of treatment) to Month 13 and from baseline to Month 13 in: fasting (prebreakfast) SMPG and change in average SMPG values based on 4-point SMPG profiles, and daily basal insulin doses 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 alanine aminotransferase, 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 antibody sampling times and bioanalytical methods:

Samples for AIA assessment were to be collected at baseline (Visit 3), Week 4 (Visit 6), Month 3 (Visit 8), Month 6 (Visit 10) and Month 12 (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:

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. A mixed-effects model for repeated measures (MMRM) methodology was used to analyze change from baseline to Month 12 on key efficacy endpoints, ie, HbA_{1c}, FPG, pre-injection SMPG (average and variability) and 24-hour 8-point SMPG profile (average and variability).

Summaries of safety and tolerance results were presented by treatment group (HOE901-U300 or Lantus) for the 12-month on-treatment period and for the 4-week follow-up. Unless otherwise specified, the analysis of the safety variables is essentially 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 for the 4 week follow-up period.

Population characteristics:

A total of 811 patients with T2DM were randomized to HOE901-U300 (n=404) or to Lantus (n=407); 809 patients were exposed to IMP (safety population). The mITT population (efficacy population) included 808 patients.

Overall, a comparable number of patients in each treatment group discontinued the study treatment prematurely or received rescue therapy (HOE901-U300 88/404 [21.8%]; Lantus 92/407 [22.6%]).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 58.2 years; 190/811 patients were ≥65 years and 372/811 (45.9%) of the patients were male. The majority of patients were Caucasian (761/811; 93.8%). The mean body mass index (BMI) at baseline was 34.8 kg/m², The mean duration of diabetes prior to study start was 12.6 years, the mean duration of prior treatment with basal insulin was 3.8 years and the median daily basal insulin dose at baseline was 0.617 U/kg. Mean HbA_{1c} at baseline was 8.24%.

Rescue therapy was initiated in a similar percentage of patients in each treatment group during the 12-month on-treatment period (HOE901-U300 33/404 [8.2%]; Lantus 41/407 [10.1%]).

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 greatest decrease occurred during the first 12 weeks of treatment. The reduction in HbA_{1c} from baseline to Month 12 was comparable in the HOE901-U300 and Lantus groups (LS mean difference of HOE901-U300 versus Lantus in change from baseline to Month 12 endpoint was -0.06% [95% CI: -0.215 to 0.104]; MMRM).

Similar to the results for HbA_{1c}, the other parameters of glycemic control, such as FPG, fasting (prebreakfast) SMPG, 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. Up to the end of the 12-month on-treatment period, pre-injection SMPG continued to decrease further in the HOE901-U300 group resulting in a larger decrease compared to the Lantus group at Month 12. The other parameters remained relatively stable during the 6-month extension period in both treatment groups and mean changes from baseline to Month 12 for these parameters were similar in the HOE901-U300 and 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 from 03:00 hours to post-lunch, whereas between pre dinner and bedtime, mean plasma glucose levels were lower in the HOE901-U300 group than in the Lantus group.

The changes in glycemic control were observed while the basal insulin doses in both treatment groups were increased, mostly during the first 3-4 months and to a greater extent in the HOE901-U300 group. Mean daily basal insulin continued to increase gradually up to Month 12 in both treatment groups. At Month 12, the mean daily average insulin dose in the HOE901-U300 group (96.67 U [0.97 U/kg]) was 14% above the dose in the Lantus group (85.08 U [0.87 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 hypoglycemic event (any category at any time of day) was comparable in both treatment groups (HOE901-U300: 322/403 [79.9%]; Lantus: 337/406 [83.0%]). The percentage of patients with at least one nocturnal hypoglycemia event (any category) was lower in the HOE901-U300 group (160 patients [39.7%]) than in the Lantus group (187 patients [46.1%]). Severe hypoglycemia was reported by a low and similar percentage of patients in both treatment groups (HOE901-U300: 1.7%; Lantus: 1.5%). Hypoglycemia events occurred after rescue therapy initiation in 7 patients treated with HOE901-U300 and in 3 patients treated with Lantus.

A total of 6 patients died during the study (4 patients [1.0%] in the HOE901-U300 group and 2 patients [0.5%] in the Lantus group) due to treatment-emergent adverse events (TEAEs). The deaths were not considered to be related to the study drug, except for the fatal event of acute myocardial infarction (HOE901-U300 group) in a patient with cardiovascular history. The event was reported to possibly be related to the IMP or to the NIMP by the Investigator, as it could not have been excluded given the sudden and unexpected nature of the event.

The percentage of patients experiencing any TEAE was higher in the HOE901-U300 group (278 patients [69.0%]) than in the Lantus group (244 patients [60.1%]), with no single system organ class contributing to this difference. The percentage of patients with serious TEAEs (30 patients [7.4%]) was the same in both treatment groups.

A similar proportion of patients in each group experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300: 2.7%; Lantus: 1.7%). Serious cardiac TEAEs were reported by a low number of patients in both treatment groups (HOE901-U300: 2.2%; Lantus 1.2%). Injection site reactions (HOE901-U300: 1.2%; Lantus 3.0%) and hypersensitivity reactions (HOE901-U300: 4.7%; Lantus: 4.9%) 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 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.

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

Four-week follow-up population:

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, which in the majority of cases was Lantus. A total of 248/811 (30.6%) randomized patients (post HOE901-U300: 116/404 patients [28.7%]; post Lantus: 132/407 patients [32.4%]) participated in the 4-week follow-up period.

During the first week of the 4-week follow-up period, the decrease in the basal insulin doses was larger in patients in the post HOE901-U300 group (-15.18%) than in patients in the post Lantus group (-3.36%). Thereafter, basal insulin dose levels remained almost unchanged up to the end of the 4-week follow-up period.

The decrease in insulin doses resulted in small increases in fasting (prebreakfast) SMPG in both treatment groups, which occurred primarily in the first 2 weeks of the follow-up period. Thereafter, up to the end of the 4-week follow-up period, mean fasting (prebreakfast) SMPG was maintained at ≤7.0 mmol/L in both groups.

Following the switch to commercial basal insulin (primarily Lantus), increased hypoglycemia was reported in the post HOE901-U300 group (38/116 patients [32.8%]) versus the post Lantus group (31/132 patients [23.5%]). The hypoglycemia events were mainly reported during daytime between 06:00 and 23:59 hours, although the increase was particularly marked for nocturnal hypoglycemia (post HOE901-U300: 10/116 patients [8.6%]; post Lantus: 7/132 patients [5.3%]). One patient (0.9%) reported severe hypoglycemia during the second week of the 4-week follow-up period in the post HOE901-U300 group.

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.

Issue date: 22-Oct-2014