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Sponsor: Sanofi **Drug substance(s):** Insulin glargine (U300)	**Study Identifiers:** U1111-1139-3894, NCT02855684 **Study code:** EFC12814
Title of the study: 6-Month, Multicenter, Randomized, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycemic Drugs	
Study center(s): 52 sites (37 sites in China, 4 sites in Taiwan and 11 sites in South Korea)	
Study period: Date first patient enrolled: 24/Aug/2016 Date last patient completed: 06/Aug/2018	
Phase of development: 3	
Objectives: Primary objective: To compare the efficacy of a new formulation of insulin glargine (HOE901- U300) and Lantus in terms of change of HbA1c from baseline to endpoint (scheduled at Month 6, Week 26) in patients with T2DM. Secondary objectives: • To compare HOE901-U300 and Lantus in terms of occurrence of hypoglycemia and nocturnal hypoglycemia; • To compare HOE901-U300 and Lantus in terms of reaching target HbA1c values (all and reaching target without hypoglycemia); • To compare HOE901-U300 and Lantus in terms of controlled plasma glucose (all and reaching target without hypoglycemia); • To compare the frequency of occurrence and diurnal distribution of hypoglycemia by category of hypoglycemia (documented symptomatic, asymptomatic, nocturnal, severe, probable and relative); • To assess the safety and tolerability of HOE901-U300; • To assess the development of anti-insulin glargine antibodies.	
Methodology: The randomization was in a 2:1 ratio (HOE901-U300 versus Lantus) and was stratified according to HbA1c values at screening (<8.0%; ≥8.0%), use of sulfonylurea or glinides (yes versus no) and geographical region (non-China; China). The sample size (600 patients: 400 with HOE901-U300 and 200 with Lantus) was chosen to ensure sufficient power for the primary endpoint (change in HbA1c from baseline to endpoint).	
Number of patients: Planned: 600 (400 with HOE901-U300 and 200 with Lantus) Randomized: 604 (401 with HOE901-U300 and 203 with Lantus) Treated: 598 (397 with HOE901-U300 and 201 with Lantus) **Evaluated:** Efficacys: 598 (397 with HOE901-U300 and 201 with Lantus) Safety: 598 (397 with HOE901-U300 and 201 with Lantus)	
Diagnosis and criteria for inclusion: Inclusion criteria: Adult patients with T2DM inadequately controlled with non-insulin antihyperglycemic drug(s); Signed written informed consent. Main exclusion criteria: Age <legal age of adulthood at the time of	

screening; HbA1c <7.0% (<53 mmol/mol) or >11% (>97 mmol/mol) (at screening); History of T2DM for less than 1 year before screening; Less than 6 months before screening with non-insulin antihyperglycemic treatment; Change in dose of non-insulin antihyperglycemic treatment in the last 3 months before screening; Initiation of new glucose-lowering medications and/or weight loss drug in the last 3 months before screening visit and/or initiation of glucagon like peptide-1 (GLP-1) receptor agonist in the last 6 months before screening visit ; Patients receiving only non-insulin antihyperglycemic drugs not approved for combination with insulin according to local labeling (Note: non-insulin antihyperglycemic drugs not approved for combination with insulin are to be discontinued at randomization); Current or previous insulin use except for a maximum of 10 consecutive days (eg, acute illness, surgery) during the last year prior to screening; History of hypoglycemia unawareness, severe hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis during the previous 6 months; Unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require treatment (eg, laser, surgical treatment or injectable drugs) during the study period.

Study treatments

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

Formulation: HOE901-U300 (300 U/mL insulin glargine solution) is a sterile, non-pyrogenic, clear, colorless solution in a 1.5 mL cartridge containing in total 450 units of insulin glargine. Lantus (100 U/mL insulin glargine solution) is a sterile, non-pyrogenic, clear, colorless solution in a 3 mL cartridge containing in total 300 units of insulin glargine.

Route(s) of administration: Subcutaneous injection

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

Starting dose: The initial daily dose of basal insulin in both treatment groups (HOE901-U300 and Lantus) was 0.2 U/kg body weight (BW).

The basal insulin dose was adjusted once weekly, but no more often than every 3 days to achieve a target fasting SMPG in the range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) according to dose adjustment schedule shown in the below table.

Insulin glargine dose adjustment schedule

Lantus or HOE901-U300 dose adjustment schedule	
Median of fasting self-monitored plasma glucose (SMPG) from last 3 days (including current day) in the range of	Dose adjustment Lantus or HOE901-U300 (U)
≥ 180 mg/dL (10 mmol/L)	+ 6
≥140 mg/dL and <180 mg/dL (≥7.8 mmol/L and <10.0 mmol/L)	+ 4
>100 mg/dL and <140 mg/dL (>5.6mmol/L and <7.8 mmol/L)	+ 2
Glycemic target: fasting SMPG between 100 and 80 mg/dL (5.6 and 4.4 mmol/L), inclusive	No change
<80 mg/dL and ≥60 mg/dL (<4.4 and ≥3.3 mmol/L)	- 2
<60 mg/dL (<3.3 mmol/L) or occurrence of ≥2 symptomatic or 1 severe hypoglycemia episode in the preceding week	- 2 to - 4 or at the discretion of the investigator

Noninvestigational medicinal product(s) (if applicable):

Patients in both treatment groups continued with their non-insulin antihyperglycemic drug(s) during the study. The type and dose remained unchanged during the study, unless identified safety concerns necessitate a reduction in dose or discontinuation of non-insulin antihyperglycemic drug(s).

Non-insulin antihyperglycemic drug(s) not approved in combination with insulin according to local labeling, if used, were discontinued at randomization.

Rescue treatment:

If patient's glycemic control was not improved under the threshold values (HbA1c >10% at Week 12, FPG >200 mg/dL or HbA1c >8.4 % from Week 12 to the end of the study), and no reasonable explanation existed for insufficient glucose control, or if appropriate action failed to decrease FPG/HbA1c under the threshold values, intensification of the treatment was to be considered using a non-investigational medicinal product (NIMP). The choice of the anti-diabetic treatment added to the basal insulin was based on Investigator's decision and local treatment guidelines, adding a prandial insulin was to be the preferred option.

Duration of treatment: 26 weeks

Duration of observation: Up to 29 weeks (an up to 2-week screening period, a 26-week treatment period, a 2-day [till 4 days] post-treatment safety follow-up period).

Criteria for evaluation:

Efficacys:

Primary endpoint: Change in HbA1c from baseline to endpoint (Month 6, Week 26)

Secondary endpoints:

- Incidence (%) of patients with at least one hypoglycemia, indicated as severe and/or confirmed by plasma glucose ≤70 mg/dL (3.9 mmol/L) that occurred at any time of a day, during the entire treatment period;
- Incidence (%) of patients with at least one nocturnal hypoglycemia, indicated as severe and/or confirmed by plasma glucose ≤70 mg/dL (3.9 mmol/L) that occurred between 00:00 and 05:59 hours, regardless whether patient was awake or woke up because of the event, during the entire treatment period.
- Incidence (%) of patients with at least one hypoglycemia, indicated as severe and/or confirmed by plasma glucose <54 mg/dL (3.0 mmol/L) that occurred at any time of a day, during the entire treatment period;
- Incidence (%) of patients with at least one nocturnal hypoglycemia, indicated as severe and/or confirmed by plasma glucose <54 mg/dL (3.0 mmol/L) that occurred between 00:00 and 05:59 hours, regardless whether patient was awake or woke up because of the event, during the entire treatment period;
- Proportion (%) of patients with HbA1c <7 % and ≤6.5 %
  - at endpoint;
  - at endpoint having experienced no hypoglycemia event during the last 12 weeks of the treatment period.
- Proportion (%) of patients with FPG <100 mg/dL (5.6 mmol/L) and ≤120 mg/dL (6.7 mmol/L)
  - at 12 weeks and at endpoint;
  - at 12 weeks having experienced no hypoglycemia event during the last 4 weeks before visit 15;
  - at endpoint having experienced no hypoglycemia event during the last 4 weeks of the treatment period.
- Proportion of patients requiring rescue therapy
- Change in fasting plasma glucose (FPG) from baseline to endpoint.
- Change in 8-point SMPG profiles per time-point from baseline to endpoint including change of nocturnal SMPG;
- Change of mean 24-hour plasma glucose (mmol/L) (based on 8-point SMPG) from baseline to endpoint;
- Change in variability of mean 24-hour plasma glucose (mmol/L) based on 8-point SMPG from baseline to endpoint (month 6 [week 26]) calculated as coefficients of variation of the 8-point SMPG profiles;

- Change in daily basal insulin dose (U/day and U/kg body weight [BW]/day) from baseline to endpoint.

Safety endpoints:

- Hypoglycemia events
- Local tolerability at injection site,
- Hypersensitivity reactions
- Adverse events including serious adverse events (SAEs) and adverse events of special interest (AESIs)
- Clinical laboratory data
- Vital signs including BW
- Electrocardiogram (ECG)
- Anti-insulin glargine antibodies (AIAs)

Anti-insulin antibody sampling times and bioanalytical methods: Blood samples for AIAs were taken at 4 visits (Visit 3, Visit 7, Visit 15 and Visit 18). They were determined at a centralized laboratory using a validated anti-insulin antibody binding assay methodology.

Statistical methods:

The primary efficacy endpoint and all secondary efficacy endpoints were summarized using the mITT population (all randomized patients who received at least one dose of the open label study drugs, and had both a baseline assessment and at least one post baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures).

Any missing efficacy endpoint values (month 6, week 26) were imputed from the last available post-baseline value using last observation carried forward (LOCF) method. For all patients rescued during the 6-month on-treatment period, the last post-baseline HbA1c measurement before the rescue and during 6-month on-treatment period was used

The primary efficacy variable (change in HbA1c from baseline to endpoint in %) was analyzed, using an analysis of covariance (ANCOVA) model with treatment, randomization strata of screening HbA1c (<8.0 and ≥8.0%), use of sulfonylurea or glinides (yes; no) and geographical region (Non-China; China) as fixed effects, and using the HbA1c baseline value as a covariate. Differences between HOE901-U300 and Lantus and two-sided 95% confidence intervals were estimated within the framework of ANCOVA.

A stepwise closed testing approach was used for the primary efficacy variable to assess non-inferiority and superiority sequentially. Step 1 proceeded to assess non-inferiority of HOE901-U300 versus Lantus in the primary endpoint; non-inferiority was demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on mITT population was <0.4%; the testing stopped if the non-inferiority was not demonstrated. Step 2 and 3 tested the superiority of HOE901-U300 over Lantus on selected secondary efficacy endpoints (incidence of patients with at least one hypoglycemia/nocturnal hypoglycemia, indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) that occurred at any time of a day, during the 6-month on-treatment period); the testing stopped as soon as an endpoint was found not statistically significant at one-sided $\alpha = 0.025$ level. Step 4 tested the superiority of HOE901-U300 over Lantus in the primary endpoint; the superiority was demonstrated if the upper bound of the two-sided 95% CI for the difference between HOE901-U300 and Lantus on mITT population was < 0 (zero).

The summary of safety and tolerability results were presented by treatment group. All safety analyses were performed on the safety population (all patients randomized and exposed to at least one dose of IMP, regardless of the amount of treatment administered).

Summary:

Population characteristics:

A total of 604 patients with type 2 diabetes mellitus inadequately controlled with non-insulin antihyperglycemic drug(s) were randomized to HOE901-U300 (401 patients) or to Lantus (203 patients); 598 patients were exposed to investigational medicinal product (IMP) (safety population). The mITT population (efficacy population) included 598 patients.

Overall, During the 6-month on treatment period, the percentage of patients who permanently discontinued treatment was 5.5% in the HOE901-U300 group and 3.0% in the Lantus group. A total of 375 (93.5%) patients in the HOE901-U300 group and 195

(96.1%) patients in the Lantus group completed the 6-month treatment period.

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 58.3 years; the majority of the patients (72.2%) were <65 years. Overall, 56.6% of the patients were male. The mean BMI at baseline was 25.23 kg/m²; at baseline, 7.2% of the patients had a BMI ≥30 kg/m2. The mean duration of diabetes prior to study start was 10.63 years (median: 9.82 years). The average daily basal insulin starting dose at baseline was comparable in both treatment groups (HOE901-U300: 12.16 U [0.179 U/kg]; Lantus: 12.27 U [0.180 U/kg]).).

Mean HbA1c at baseline was 8.60% in the HOE901-U300 group and 8.53% in the Lantus group.

Efficacy results:

Primary endpoint:

At Week 26 (LOCF endpoint), mean HbA1c was comparably decreased to around 7.0% in both treatment groups (7.04% in the HOE901-U300 group and 7.00% in the Lantus group). The LS mean difference between HOE901-U300 and Lantus was 0.02%, (95% CI: -0.101% to 0.143%). The non-inferiority of HOE901-U300 compared to Lantus in terms of change of HbA1c from baseline to Week 26 endpoint (LOCF) was demonstrated as the upper bound of the 2-sided 95% CI of the LS mean difference between HOE901-U300 and Lantus was below the pre-specified non-inferiority margin of 0.4%. The LS mean changes from baseline to Week 26 (LOCF) in HbA1c were -1.45% (95% CI: -1.548% to -1.350%) for the HOE901-U300 group and -1.47% (95% CI: -1.592% to -1.348%) for the Lantus group.

Secondary endpoints:

The incidence of patients (%) with at least one severe and/or confirmed (ie, plasma glucose ≤3.9 mmol/L [70 mg/dL]) hypoglycemia occurring at any time of a day during the 6-month on treatment period was numerically lower in the HOE901-U300 group (68.0%) compared to the Lantus group (72.6%), although the difference was not statistically significant (p-value=0.2838). The pre-specified analysis did not show superiority of HOE901-U300 over Lantus (RR versus Lantus = 0.94 [95% CI: 0.85 to 1.05]; p = 0.2838).

The incidence of patients (%) with at least one severe and/or confirmed (ie, plasma glucose ≤3.9 mmol/L [70 mg/dL]) nocturnal hypoglycemia (between 00:00 and 05:59) during the 6-month on-treatment period was numerically lower in the HOE901-U300 group compared to the Lantus group (37.3% vs 44.8%; RR versus Lantus = 0.84 [95% CI: 0.70 to 1.02]).

The incidence of patients (%) with at least one severe and/or confirmed (ie, plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia at any time of a day was generally comparable between the HOE901-U300 group (9.3%) and the Lantus group (11.9%).

The incidence of patients (%) with at least one severe and/or confirmed (ie, plasma glucose <3.0 mmol/L [54 mg/dL]) nocturnal hypoglycemia (between 00:00 and 05:59) was also generally comparable between the HOE901-U300 group (5.5%) and the Lantus group (4.0%) in the HOE901-U300 group.

The percentage of patients who reached HbA1c <7% at Month 6 was similar in both treatment groups (51.1% in the HOE901-U300 group and 52.2% in the Lantus group). The percentage of patients who reached this target at Month 6 without any episode of hypoglycemia during the last 12 weeks of the treatment period was also similar in the HOE901-U300 group (19.1%) and in the Lantus group (21.9%).

Similar observation was made for the percentage of patients who reached HbA1c ≤6.5% at Month 6, and for the percentage of patients who reached HbA1c ≤6.5% at Month 6 without any episode of hypoglycemia during the last 12 weeks of the treatment period.

A comparable percentage of patients reached target central laboratory FPG <5.6 mmol/L (100 mg/dL) at Month 6 in the HOE901-U300 and Lantus groups (20.2% and 23.4%, respectively). Similarly, there was no meaningful difference between the treatment groups when considering the percentage of patients who reached this target without experiencing any hypoglycemia (9.8% versus 11.4%, respectively) during the last 4 weeks of the treatment period.

The proportion of patients who had FPG ≤6.7 mmol/L (120 mg/dL) at Month 6 was 57.2% in the HOE901-U300 group and 64.2% in the Lantus group. The percentage of patients reaching this target with no hypoglycemia during the last 4 weeks of the treatment period was 32.7% in the HOE901-U300 group and 38.8% in the Lantus group.

No patient in either treatment groups required rescue therapy during the 6-month on-treatment period.

The LS mean changes from baseline to Month 6 (LOCF) endpoint in FPG were comparable in both treatments groups. In both treatment groups, almost whole decrease in FPG occurred during the first 12 weeks. Thereafter and up to Month 6, FPG was generally stable in both groups.

The 8-point SMPG profiles (mean SMPG over all patients at each time point) in the HOE901-U300 and Lantus groups were comparable between treatment groups at both baseline and Month 6. The profiles show in both treatment groups a marked decrease in plasma glucose at all time points at Month 6 compared with baseline. The mean change in 24-hour average plasma glucose and in the variability of mean 24-hour plasma glucose both showed similar results between two treatment groups.

An increase in mean daily basal insulin dose (U) was observed in both treatment groups, primarily during the first 12 weeks when most titration was done, with a greater increase in the HOE901-U300 group compared to the Lantus group. At Month 6 (LOCF), the mean daily basal insulin dose increased to 24.20 U [0.34 U/kg] in the HOE901-U300 group and to 20.86 U [0.29 U/kg] in the Lantus group. The LS mean change from baseline to Month 6 (LOCF) in daily dose of basal insulin was higher in the HOE901-U300 group than in the Lantus group (HOE901-U300: 11.96 U, 0.16 U/kg; Lantus: 8.48 U, 0.11 U/kg).

Safety results:

During the treatment emergent adverse event (TEAE) period, there was a trend to lower percentages of patients reporting at least one hypoglycemia event of any category among patients treated with HOE901-U300 than with Lantus. This trend was also observed for most categories of hypoglycemia.

Similarly to hypoglycemia at any time of a day, nocturnal hypoglycemia (between 00:00 and 05:59) was reported by a numerically lower proportion of patients in the HOE901-U300 group compared with the Lantus group in categories of any hypoglycemia, documented symptomatic hypoglycemia ≤3.9 mmol/L (70 mg/dL) and/or severe and/or confirmed hypoglycemia ≤3.9 mmol/L (70 mg/dL).

Results for nocturnal hypoglycemia by sleep status were consistent to those of nocturnal hypoglycemia occurring between 00:00 and 05:59. The overall percentage of patients with at least one hypoglycemia event during daytime (between 06:00 and 23:59) also showed a similar pattern as the nocturnal hypoglycemia between 00:00 and 05:59.

During the first 8 weeks of study treatment, there was a trend for a numerically lower incidence of patients in the HOE901-U300 group reporting at least one hypoglycemia event at any time of a day in most hypoglycemia categories compared to the Lantus group. This trend was consistently observed also during the first 12 weeks of treatment, which corresponded to the period with the steepest increase of the basal insulin dose in both treatment groups (titration period). A generally similar pattern was observed for nocturnal hypoglycemia (between 00:00 and 05:59).

Descriptive analyses of events per patient-year of exposure showed comparable or lower rates of hypoglycemia in the HOE901-U300 group compared with the Lantus group. For nocturnal hypoglycemia (occurring between 00:00 and 05:59) and daytime hypoglycemia (between 06:00 and 23:59), the event rate per patient-year in category of any hypoglycemia event tended to be lower in the HOE901-U300 group than in the Lantus group.

The number and incidence of patients reporting at least one severe hypoglycemia was low: no patient in the HOE901-U300 group reported severe hypoglycemia and one patient in the Lantus groups (1 of 201 patients [0.5%]) reported one event during daytime. This event met seriousness criteria and was reported as SAE.

A total of 197 (49.6%) patients in the HOE901-U300 group and 100 (49.8%) patients in the Lantus group reported TEAEs.

Two patients (0.5%) in the HOE901-U300 group and one patient (0.5%) in the Lantus group experienced TEAE leading to death. In the HOE901-U300 group, a patient with a history of coronary heart disease experienced a cardio-respiratory arrest leading to fatal outcome approximately 5 months after the first IMP administration, which was considered to be related to the study medication by the Investigator; another patient experienced a gastric cancer leading to fatal outcome approximately 6 months after the first IMP administration, which was considered not to be related to the study medication by the Investigator. In the Lantus group, a patient experienced death (reported as: death of unknown cause) approximately 5.5 weeks after the first IMP administration, which was considered not to be related to the study medication by the Investigator.

The percentage of patients experiencing serious TEAEs was similar in the HOE901-U300 and Lantus groups. In total, 22 patients (5.5%) in the HOE901-U300 group and 11 patients (5.5%) in the Lantus group had at least 1 serious TEAE.

The number of patients who reported TEAE that led to permanent discontinuation of study treatment was low in both treatment groups: 5 patients (1.3%) in the HOE901-U300 group and 2 patients (1.0%) in the Lantus group.

No patient had ALT >5 ULN during the TEAE period and no patient was found to have ALT >3 ULN with total bilirubin > 2 ULN (Hy's law). One patient in the HOE901-U300 group with increased ALT values (below 3 ULN) at baseline had ALT> 3 ULN during the TEAE period.

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

The percentage of AIA positive patients increased consistently during the TEAE period and a slightly higher AIA increase was observed in the HOE901-U300 group compared to the Lantus group. There was no difference between the two treatment groups in terms of AIA titer and cross reactivity to human insulin, nor was there any difference concerning the effect of AIA on efficacy and safety endpoints, excepted that there was a trend to a higher incidence of hypoglycemia event of any type in patients with high AIA titer compared to patients with low AIA titer during the TEAE period.

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