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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glargine (HOE901)	**Study Identifiers:** NCT01349855, EudraCT 2010-023771-26 **Study code:** TDR11626
Title of the study: A randomized, double-blind, 2x2 cross-over euglycemic clamp study in two parallel cohorts to assess the safety and tolerability of two dose levels of a new formulation of insulin glargine and to compare its pharmacodynamic and pharmacokinetic properties with 0.4 U/kg/day Lantus® in an 8-days multiple dosing regimen in patients with diabetes mellitus type 1	
Study center(s): One center in Germany	
Study period: Date first patient enrolled: 28 March 2011 Date last patient completed: 28 May 2011	
Phase of development: Phase 1 (exploratory)	
Objectives: • To assess the safety and tolerability of two dose levels of HOE901-U300 in a once-daily multiple dosing regimen • To compare the pharmacokinetic (PK) and pharmacodynamic (PD) properties of two dose levels of HOE901-U300 with 0.4 U/kg Lantus® in a once-daily multiple dosing regimen	
Methodology: A single-center, randomized, double-blind, 2-treatment (investigational 300 U/mL insulin glargine versus active comparator 100 U/mL insulin glargine [Lantus]), 2-period, 2-sequence, cross-over, euglycemic clamp study in 2 parallel dose cohorts, in a multiple (8-day once-daily) dosing regimen, in patients with type 1 diabetes mellitus (T1DM).	
Number of patients: Planned: 30 Randomized: 30 Treated: 30 **Evaluated:** Pharmacodynamics: 30 Safety: 30 Pharmacokinetics: 30	
Diagnosis and criteria for inclusion: Male or female patients aged 18 to 65 years with diabetes mellitus type 1 (T1DM) for more than one year.	

Study treatments

Investigational (test [T]) product: Insulin glargine solution for injection 300 U/mL (HOE901-U300).

Dose: 0.4 U/kg (Test 1 [T1] treatment) in Cohort 1; 0.6 U/kg (T2 treatment) in Cohort 2.

Administration: Once daily (QD), 8 days in one treatment period (TP), subcutaneously (SC), periumbilically.

Reference (R) therapy: Commercially available insulin glargine solution for injection 100 U/mL (Lantus U100).

Dose: 0.4 U/kg in both cohorts (Reference 1[R1] treatment in Cohort 1; Reference 2 [R2] treatment in Cohort 2).

Administration: QD, 8 days in one TP, SC, periumbilically.

Duration of treatment: 8 days in one of the two TPs

Duration of observation: 33 to 68 days (screening 3 to 21 days, 2 TPs of 10 days [8 dosing days followed by a 36-hour clamp], washout period of 7 to 21 days between TP1 and TP2, follow-up till end-of-study [EOS] visit 7 to 10 days after last dosing)

Criteria for evaluation:

Pharmacodynamic: None of the PD variables was defined as primary. The following secondary PD variables were derived:

- Area under the body-weight-standardized glucose infusion rate (GIR) time curve up to 24 hours (h) after dosing (GIR-AUC_{0-24} [mg/kg]);
- Area under the body weight standardized GIR time curve up to 36 h after dosing (GIR-AUC_{0-36} [mg/kg]);
- Time (h) to 50% of GIR-AUC_{0-24} (T50%-GIR-AUC_{0-24} [h]);
- Time (h) to 50% of GIR-AUC_{0-36} (T50%-GIR-AUC_{0-36} [h]);
- Maximum smoothed body weight standardized GIR (GIR_{max} [mg*min/kg]);
- First time after dosing to reach GIR_{max} (GIR-T_{max} [h]);
- Time at clamp level (time to elevation of smoothed blood glucose [BG] profile above clamp level, “duration of euglycemia”) was to be calculated as the time from dosing to the last value of the smoothed BG concentration curve at or below 105 mg/dL;
- Durations of controlled BG within predefined margins was defined as the time from dosing to the last value of the smoothed BG concentration curve at or below 110 mg/dL, 130 mg/dL, or 150 mg/dL;
- To evaluate the variability of BG control over time of the two treatment formulations, the means of the individual CV% was to be calculated per treatment.

Safety: Adverse events (AEs) reported by the patient or noted by the Investigator, hypoglycemic episodes as classified by the American Diabetes Association (ADA) (severe, documented symptomatic, asymptomatic, probable symptomatic, and relative hypoglycemia) and nocturnal hypoglycemia, vital signs, physical examination, standard hematology and blood chemistry parameters, urinalysis, electrocardiogram (ECG; 12-lead and telemetry), local tolerability at the SC injection site, and anti-insulin antibodies.

Pharmacokinetics: The following PK parameters were calculated, using non-compartmental methods for insulin glargine serum concentrations after multiple dosing in steady state:

- Maximum serum concentration observed (INS-C_{max});
- First time to reach INS-C_{max} (INS-T_{max});
- Area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to 24 hours post dosing on Day (D)8 (INS-AUC_{0-24});
- Area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to 36 hours post dosing on D8 (INS-AUC_{0-36});
- Time to 50% of INS-AUC_{0-24} ($T_{50\%}$-INS- AUC_{0-24});
- Time to 50% of INS-AUC_{0-36} ($T_{50\%}$-INS- AUC_{0-36}).

Pharmacokinetic sampling times and bioanalytical methods: Blood was collected for the determination of insulin glargine concentrations in serum at the following time points in both TPs: 0H on D1 to D7; 0H, 1H, 2H, 4H on D8; 6H, 8H, 10H, 12H, 14H, 16H, 20H, 24H, 28H on D9; 32H and 36H on D10. Insulin glargine (free form) in serum was determined using a radioimmunoassay (RIA) with a lower limit of quantification (LOQ) of 5.02 µU/mL.

Statistical methods: Statistical analyses compared test treatments T1 and T2 with reference treatment R.

Pharmacodynamics: None of the analyses was considered as primary. The analysis of secondary variables included: graphical presentations of GIR profiles; lists and descriptive statistics of derived PD parameters by cohort and treatment; treatment ratios T1/R and T2/R for GIR-AUC_{0-24}, GIR-AUC_{0-36}, and GIR_{max} (using a linear mixed effects model for log transformed data by cohort); treatment differences T1-R and T2-R for $T_{50\%}$-GIR-AUC_{0-24}, $T_{50\%}$-GIR-AUC_{0-36}, GIR-t_{max}, and duration of euglycemia and BG control (using nonparametric analysis based on Hodges-Lehmann method and graphically by cohort); lists and descriptive statistics of the performance of clamp parameters by cohort and treatment, and PD subset analyses. The analyses were conducted on the PD population (all patients with no important deviations related to Investigational Medicinal Product [IMP] intake and/or PD measurements and for whom the PD parameters were available and evaluable).

Safety: The safety analysis was based on the review of individual values (clinically significant abnormalities) and descriptive statistics by treatment. For AEs, frequencies of treatment-emergent adverse events (TEAEs), coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0) and classified by system-organ classes (SOC) and preferred term (PT), were tabulated by treatment. All AEs were listed. Hypoglycemic episodes, as per the ADA classification and nocturnal, were listed and their frequencies summarized by treatment. Clinical laboratory data were listed and analyzed using descriptive statistics and potentially clinically significant abnormalities (PCSAs) for each type of measurement and by treatment. For vital signs and ECG, frequencies of patients with abnormalities and PCSAs were summarized by treatment. Frequencies for signs of local intolerance were analyzed by treatment. Anti-insulin-glargine antibodies were analyzed for status (positive/negative), cross-reactivity to human insulin, and titers/concentrations by visit for each cohort. The analyses were conducted on the safety population (all patients who were exposed to study treatment, regardless of the amount of treatment administered).

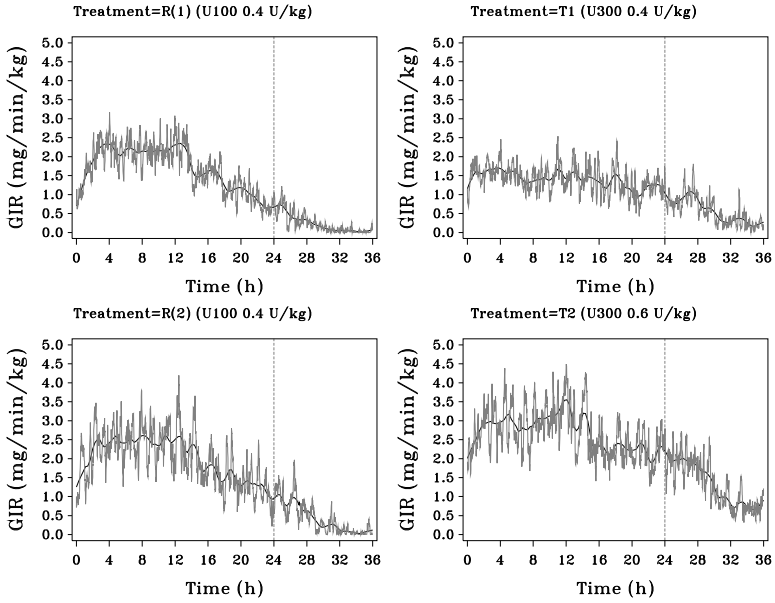
Pharmacokinetics: PK parameters were summarized by cohort and treatment, and additionally for treatment R pooled over Cohorts 1 and 2, using descriptive statistics. Statistical analyses were provided separately for each cohort and compared test treatments (T1 or T2) with reference treatment (R) of the respective cohort, namely R1 for Cohort 1 and R2 for Cohort 2 (comparisons between T1 and R1 were considered main comparisons and those between T2 and R2 subordinated). Analysis of treatment ratios for INS-AUC_{0-24}, INS-AUC_{0-36}, and INS-C_{max} was performed using a linear mixed effects model for log transformed data. Estimate and 90% and 95% confidence intervals (CIs) for the treatment ratios of geometric means (T1/R1, T2/R2) were provided. Pairwise treatment comparisons for $T_{50\%}$-INS-AUC_{0-36} and $T_{50\%}$-INS-AUC_{0-24} were analyzed non-parametrically based on Hodges-Lehmann method. Dose-exposure and PK/PD relationships were explored graphically.The analyses were conducted on the PK population (all patients with no important deviations related to IMP intake and/or related to PK sampling).

Summary:

Pharmacodynamic results: The overall PD effects of the reference therapy (0.4 U/kg Lantus U100) in both groups were generally comparable, displaying a modest rise and fall in activity (GIR) within 24 hours after dosing and wearing off quickly beyond.

The PD effects of 0.4 U/kg HOE901-U300, by contrast, displayed a more evenly balanced profile without a rise in activity (GIR) within 24 hours and extending beyond. The PD effects of 0.6 U/kg HOE901-U300 were greater than with 0.4 U/kg Lantus U100 within 24 hours and beyond (see the figure below).

Mean glucose infusion rate profiles



Patients required less glucose (as measured by GIR-AUC) on 0.4 U/kg HOE901-U300 than with 0.4 U/kg Lantus U100 to maintain BG control within the first 24 hours of the clamp period, but catching up beyond 24 hours to result in a total GIR-AUC until clamp end at 36 hours comparable to reference treatment. For 0.4 U/kg HOE901-U300, the ratios of geometric means of its GIR-AUC over those of the reference treatment were 0.73 (90% CI: [0.56; 0.94]) and 0.85 (90% CI: [0.70; 1.03]) for 24 hours and 36 hours, respectively.

Patients on 0.6 U/kg HOE901-U300 required more glucose than with 0.4 U/kg Lantus U100 to maintain BG control during clamp within 24 hours and beyond. For 0.6 U/kg HOE901-U300, the ratios of geometric means of its GIR-AUC over those of 0.4 U/kg Lantus U100 were 1.46 (90% CI: [0.96; 2.21]) and 1.65 (90% CI: [1.11; 2.46]) for 24 hours and 36 hours, respectively.

With HOE901-U300, a dose of 0.4 U/kg resulted in a lower and a dose of 0.6 U/kg in a higher mean GIR_{max} than with 0.4 U/kg Lantus U100. The estimates for the ratios of geometric means (T1/R1 and T2/R2) were 0.81 (90% CI: [0.68; 0.97]) and 1.20 (90% CI: [0.88; 1.62]), respectively.

The more evenly balanced GIR profiles of HOE901-U300 are also displayed by the times to 50% of GIR-AUC (T50%-GIR-AUC) within 24 and 36 hours, respectively, and the straightened cumulative GIR-AUC profile within 0 – 36 hours.

The means of T50%-GIR-AUC over 36 hours were longer with HOE901-U300 at doses of 0.4 and 0.6 U/kg by around 3 and 2 hours, respectively, as compared to 0.4 U/kg Lantus U100. Over 24 hours, this parameter was prolonged at 0.4 U/kg HOE901-U300 by about 1.5 hours (compared to R1), whereas it was nearly unchanged in dose cohort 2 at 0.6 U/kg HOE901-U300 in comparison to the reference treatment (R2) of 0.4 U/kg Lantus.

The individual fluctuations of the smoothed GIR profiles (GIR-smFL$_{(0\text{-}24h)}$ and GIR-smFL$_{(0\text{-}36h)}$) were lower with HOE901-U300 at both dose levels as compared to Lantus U100, with mean values (SD) of 0.43 (0.19) versus 0.61 (0.23) mg/kg/min and 0.60 (0.21) versus 0.69 (0.42) mg/kg/min over 24 hours and 0.56 (0.29) versus 0.84 (0.36) mg/kg/min and 0.82 (0.34) versus 0.92 (0.42) mg/kg/min over 36 hours in the two dose cohorts, respectively.

During the clamp period, BG was tighter and longer controlled with both doses of HOE901-U300 than with 0.4 U/kg Lantus U100 as indicated by the mean cumulative times of blood glucose within predefined targets at or below 110, 130 and 150 mg/dL, as well as at or below the level of euglycemia (≤105 mg/dL). The end of activity as determined by the duration to last smoothed BG at or below these thresholds was later for both dose levels of HOE901-U300 than for 0.4 U/kg Lantus U100.

More patients in both dose cohorts had continuous blood glucose control at or below the thresholds of 110, 130 and 150 mg/dL over 36 hours under HOE901-U300 (both dose levels) than under 0.4 U/kg Lantus U100. Over 24 hours, continuous blood glucose control at these thresholds was found in more patients under 0.6 U/kg HOE901-U300 than under the reference treatment, but in more patients under 0.4 U/kg Lantus than under 0.4 U/kg HOE901-U300. Two patients, both in Cohort 1, displayed the dawn phenomenon in both TPs in the morning hours on the day after last dosing (Day 9) with a temporary rise of BG while GIR was 0. This did not require counteractivities and both patients returned back to euglycemia in both cohorts. One patient in Cohort 2 on 0.4 U/kg Lantus U100 developed hyperglycemia beyond the intervention threshold of 250 mg/dL before the end of clamp which required glulisine infusion at 27 hours after dosing.

Safety results: Overall, both doses of HOE901-U300 and 0.4 U/kg Lantus U100 were well tolerated. There were no SAEs and no deaths in this study. The fraction of patients with TEAEs was the same under 0.6 U/kg HOE901-U300 as under 0.4 U/kg Lantus U100 (both 83.3%), whereas it was lower than with the reference treatment under 0.4 U/kg HOE901-U300 (64.7%). Second after hypoglycemia events, which are described separately below, headache was the most frequently reported treatment emergent adverse event (TEAE), reported in 3 of 30 patients under treatment with Lantus U100.

One male patient of the first cohort (45 years of age) had an episode of 4 ventricular extrasystoles (ventricular run) on Day 8 about 2 hours after dosing in his first period, where he had received 0.4 U/kg Lantus U100. No electrolyte abnormalities were reported. This TEAE was classified as mild and not drug-related. The patient was withdrawn after Period 1. Cardiologic assessment did not reveal any underlying cardiac condition/disease in this patient.

A female patient of Cohort 2 (52 years of age) had an episode of ventricular tachycardia about 21 hours after her last dose in the first period, where she received 0.4 U/kg Lantus U100. No electrolyte abnormalities were reported. This AE was also classified as mild and not drug-related. The patient continued the study with its second period.

Overall, the numbers/percentages of patients affected by hypoglycemia were comparable between all 3 treatments, but the number of events in relation to the cohort size was larger under 0.6 U/kg HOE901-U300 (96 events in a cohort with 12 patients) than under 0.4 U/kg Lantus U100 (188 events in 30 patients), whereas it was lower for 0.4 U/kg HOE901-U300 (88 events in a cohort of 17 patients) than with the reference therapy.

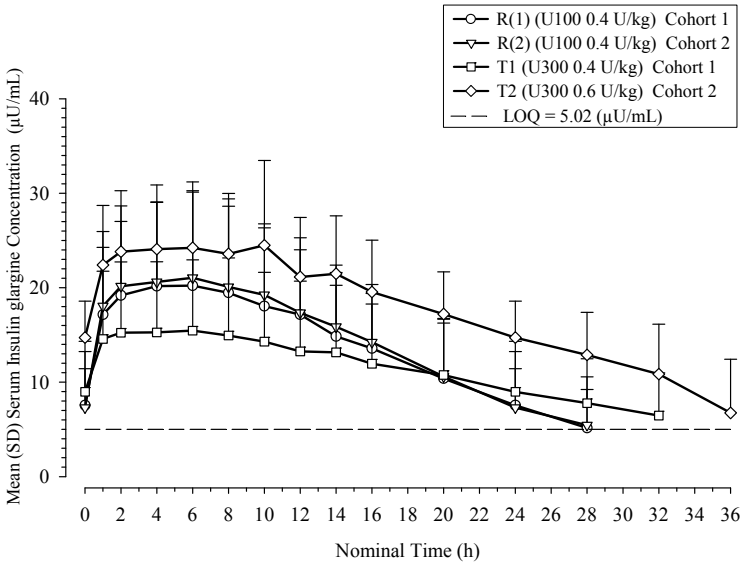
There were 2 events of severe hypoglycemia in two patients, which both occurred under HOE901-U300. These 2 events were nocturnal and both occurred in the first half of the respective TP: One on about 6 hours after dosing of Day 4 under 0.4 U/kg HOE901-U300 and the other at about 9 hours after dosing of Day 2 under 0.6 U/kg HOE901-U300. Both events were treated with 1 mg Glucagon intramuscularly.

The percentage of patients affected by nocturnal hypoglycemia was lower under 0.4 U/kg HOE901-U300 (58.8%) than under 0.4 U/kg Lantus U100 (86.7%) and under 0.6 U/kg HOE901-U300 (83.3%).

There were only few PCSA occurrences in laboratory parameters, vital signs or ECG parameters, none of clinical relevance and with no relevant differences between treatments with HOE901-U300 and Lantus U100.

Pharmacokinetic results: The steady state profiles of serum insulin glargine for treatments with HOE901-U300, T1 (0.4 U/kg) and T2 (0.6 U/kg), were generally flat from 1 hour to16 hour post dose, and displayed detectable exposure and corresponding mean serum concentrations until 32 and 36 hours post dosing, respectively (see the figure below).

Mean (+SD) insulin glargine concentration time profiles starting with dosing on Day 8 (linear scale)



Source = PKS Study : TDR11626; Scenario: S-D-A-EV-OD, Version 2

The mean serum concentrations of insulin glargine for the reference treatments with Lantus U100, R1 Cohort 1 and R2 Cohort 2, at a daily dose of 0.4 U/kg were nearly congruent with each other and displayed a small peak in comparison to the U-300 profiles. Serum concentrations were quantifiable until 28 hours after SC administration of Lantus U100.

The flatter, more constant profiles of the HOE901-U300 treatments compared to the Lantus reference treatments were reflected in a prolonged INS-$t_{1/2z}$ of 19.0 and 17.7 hours for the treatments T1 (0.4 U/kg HOE901-U300) and T2 (0.6 U/ kg HOE901-U300) compared to 13.5 and 10.8 hours for the reference treatments R1 and R2 of 0.4 U/kg Lantus each. This is also reflected in INS-C_{max}. INS-C_{max} was about 20% lower for T1 compared to R1 and about 20% higher for T2 compared to R2. The point estimates of the ratios for INS-C_{max} were 0.78 (90% CI: [0.68; 0.91]) at 0.4 U/kg (T1/R1) and 1.22 (90% CI: [0.89; 1.68]) for T2/R2, respectively.

The 24 hour exposure after repeated dosing (INS-AUC_{0-24}) was slightly lower on T1 (HOE901-U300 0.4 U/kg) compared to the reference treatment R1 (Lantus 0.4 U/kg, Cohort 1), and higher on T2 (HOE901-U300 0.6 U/kg) compared to the reference treatment R2 (Lantus 0.4 U/kg, Cohort 2). The point estimates of INS-AUC_{0-24} ratios were 0.83 (90% CI: [0.69; 1.00]) for T1 versus R1 and 1.45 (90% CI: [1.01; 2.08]) for T2 versus R2), respectively. The exposure over the entire clamp period of 36 hours (INS-AUC_{0-36}), by contrast, was almost equivalent with either treatment in Cohort 1, with a ratio estimate of 0.93 (90%CI: [0.77;1.12]) for T1/R1, while it was higher on T2 as compared to R2 with the ratio estimate of 1.65; 90%CI: [1.15; 2.38]) for T2/R2.

The time to reach 50% of 24 hour exposure (T50%-INS-AUC_{0-24}) was similar for all treatments; the median of T50%-INS-AUC_{0-24} was about 10 hours for the treatments R1, R2 and T1, and 11 hours for T2, respectively. The time to reach 50% of the exposure over the entire clamp period (T50%-INS-AUC_{0-36}) was longer for the HOE901-U300 treatments T1 and T2 compared to the reference treatments R1 and R2 with median times of 14 hours for T1 and T2, 11 hours for R1, and 12 hours for R2, respectively.

Moreover, determination by LC-MS/MS of immunoaffinity enriched metabolites from plasma confirms equal metabolism of insulin glargine regardless of formulation. The main metabolite being 21A-Gly-human insulin, defined M1.

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