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Sponsor / Company: Sanofi **Drug substance(s):** Insulin glargine (HOE901)	**Study Identifiers:** NCT01838083, EudraCT 2012-005777-31 UTN U1111-1139-3755 **Study code:** PKD13560
Title of the study: A double-blind, randomized, two-treatment crossover bioequivalence study comparing two new insulin glargine formulations using the euglycemic clamp technique in subjects with type 1 diabetes mellitus	
Study center(s): One center in Germany	
Study period: Date first patient enrolled: 16/Apr/2013 Date last patient completed: 05/Aug/2013	
Phase of development: Phase 1	
Objectives: Primary objective: • To demonstrate equivalence in exposure to insulin glargine given as HOE901-U300 test formulation T and HOE901-U300 reference formulation R in steady state conditions after 6 once-daily subcutaneous (SC) doses of 0.4 U/kg. Secondary objectives: • To assess relative pharmacodynamic (PD) activity of the HOE901-U300 test formulation T to the HOE901-U300 reference formulation R in steady state conditions after 6 once-daily SC doses of 0.4 U/kg. • To assess the safety and tolerability of the test and reference formulations of HOE901-U300.	
Methodology: Randomized (1:1), double-blind, 2-treatment, 2-period, 2-sequence, crossover, multiple (6-day once daily) dosing regimens, single center study.	
Number of patients**:** Planned: 50 Randomized: 50 Treated: 50 **Evaluated:** Pharmacodynamics: 50 Safety: 50 Pharmacokinetics: 50	
Diagnosis and criteria for inclusion: Male or female patients aged 18 to 64 years with diabetes mellitus type 1 (T1DM) for more than 1 year. Main inclusion criteria: glycated hemoglobin (HbA_{1c}) ≤9%; total insulin dose of <1.2 U/kg/day.	

Study treatments

Investigational medicinal product(s): Insulin glargine solution for injection 300 U/mL (HOE901-U300).

Formulation:

- Test formulation (treatment T): contains 0.02 mg/mL polysorbate 20 (supplied in vials of 5 mL)
- Reference formulation (treatment R): does not contain polysorbate 20 (supplied in cartridges of 3 mL)

Route(s) of administration: SC, periumbilical

Dose regimen: 0.4 U/kg/day

Duration of treatment: 6 days (one formulation per each treatment period)

Duration of observation: 29 to 64 days (screening 3 to 21 days, 2 treatment periods of 8 days [6 dosing days followed by a euglycemic clamp], washout period 7 to 21 days between last dosing day in treatment period 1 and first dosing day in treatment period 2, follow-up till end-of-study [EOS] visit 7 to 10 days after last dosing).

Criteria for evaluation:

Pharmacodynamics: None of the PD variables were defined as primary. As predefined in the clinical study protocol and in the statistical analysis plan, the main secondary PD parameter was:

- Area under the body weight standardized glucose infusion rate (GIR) versus time curve within 24 hours after dosing on Day 6 during the clamp (GIR-AUC_{0-24}[mg/kg]).

The following additional secondary PD variables were derived:

- Time to reach at least 50% of the GIR-AUC_{0-24} ($T_{50\%}$-GIR-AUC_{0-24} [hours])
- Maximum smoothed body weight standardized GIR (GIR_{max} [mg/kg/min])
- Time to reach GIR_{max} (GIR-T_{max} [hours])
- Times of controlled blood glucose within predefined margins from dosing to specified thresholds: 5.8, 6.1, 7.2, and 8.3 mmol/L (105, 110, 130, and 150 mg/dL)
- The derivation of GIR_{max} and the time to GIR_{max} were based upon smoothed body weight standardized GIR data.

Safety: Adverse events (AE) reported by the subject or noted by the investigator, hypoglycemic episodes categorized based on the American Diabetes Association (ADA) classification (severe, documented symptomatic, asymptomatic, probable symptomatic, and relative hypoglycemia) and nocturnal hypoglycemia, vital signs, physical examination, standard hematology and blood chemistry, urinalysis, electrocardiogram (ECG; 12-lead), local tolerability at the SC injection sites, and anti-insulin antibodies (AIAs).

Pharmacokinetics: The following pharmacokinetic (PK) parameters were calculated, using non-compartmental methods for insulin glargine serum concentrations after single dose in steady state:

Primary PK variable:

- Area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to 24 hours post dosing on Day 6 (INS-AUC_{0-24})

Secondary PK variables:

- Maximum serum concentration observed (INS-C_{max})
- First time to reach INS-C_{max} (INS-T_{max})
- Time to reach 50% of INS-AUC_{0-24} ($T_{50\%}$-INS- AUC_{0-24})

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Blood was collected for the determination of insulin glargine concentrations in serum at the following time points in both treatment periods (relative dosing time): 20, 0, 1, 2, and 4 hours on Day 6, and 6, 8, 10, 12, 14, 16, 20, and 24 hours on Day 7. 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 data of treatment T with data of treatment R. No adjustments of the alpha-level were made for multiple analyses.

Pharmacodynamics: The PD analyses were performed for the PD population, ie, all subjects with no important (critical, major) deviations related to investigational medicinal product (IMP) administration and/or PD measurements and whose PD parameters were available and evaluable. PD parameters were summarized by treatment using descriptive statistics; mean GIR and median blood glucose profiles were graphically presented per treatment.

None of the PD analyses were considered as primary.

Based on natural log transformed values for the main secondary PD parameter GIR-AUC_{0-24}, as well as for GIR_{max}, the ratios of test (T) and reference (R) treatments were assessed using a linear mixed effects model. Estimate and 90% confidence interval (CI) for the ratio of geometric means between test and reference were provided for GIR-AUC_{0-24} and GIR_{max}. Time to 50% of GIR-AUC_{0-24} ($T_{50\%}$-GIR-AUC_{0-24}) was compared non-parametrically (Hodges-Lehmann type analysis) between treatment T and R. Estimate and 90% CI for location shift between treatments (T-R) was derived.

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 16.0) and classified by system organ classes (SOC) and preferred term (PT), were tabulated by treatment. All AEs were listed, including allergic reactions. Hypoglycemic episodes, as per the ADA classification and nocturnal, were listed and their frequencies summarized by treatment. Clinical laboratory data were listed and potentially clinically significant abnormalities (PCSAs) summarized by treatment. For vital signs and ECG, data were listed and analyzed using descriptive statistics and PCSAs for each type of measurement and by treatment. Levels of local tolerability at injection site were listed and frequency distributions were provided. Anti-insulin glargine antibody status (positive/negative) was listed and summarized by treatment; the listing includes the individual ratio of the AIA titer at EOS relative to the titer at baseline. The analyses were conducted on the safety population (all patients who were exposed to study treatment, regardless of the amount of treatment administered).

Pharmacokinetics: The PK analyses were performed for the PK population, ie, all subjects without any important deviation related to IMP administration, for which the PK data are considered interpretable.

PK parameters were summarized by treatment using descriptive statistics.

Primary analysis:

Based on natural log transformed INS-AUC_{0-24}, the ratios of treatment T and R were assessed using a linear mixed effects model. Estimate and 90% CI for the treatment ratios of geometric means between test and reference treatments were provided for INS-AUC_{0-24}.

Bioequivalence was concluded if the 90% CI for the treatment ratio for INS-AUC_{0-24} was fully contained within [0.8000; 1.2500].

Secondary analyses:

INS-C_{max} was analyzed using the corresponding model and method as for INS-AUC_{0-24}. Estimate and 90% CI for the treatment ratios of geometric means between treatment T and R were provided for INS-C_{max}.

Time to 50% of INS-AUC_{0-24} ($T_{50\%}$-INS-AUC_{0-24}) was compared non-parametrically (Hodges-Lehmann type analysis) between treatment T and R. Estimate and 90% CI for location shift between treatments (T-R) was derived.

Summary:

Population characteristics: Fifty subjects with T1DM were randomized in the study. The mean age was 42.1 years, 38 subjects were male and 12 female, and the mean body mass index was 25.38 kg/m^2. All subjects were treated according to the randomization schedule. No subject was prematurely withdrawn from the study and all randomized subjects were included in the PD, safety and PK populations.

Pharmacodynamic results: Descriptive statistics for GIR-AUC$_{0\text{-}24}$, GIR$_{max}$ and GIR-T$_{max}$ by treatment are provided in the table below.

Descriptive statistics for GIR-AUC$_{0\text{-}24}$, GIR$_{max}$ and GIR-T$_{max}$

	T (U300 + polysorbate)	R (U300)
GIR-AUC$_{0\text{-}24h}$ (mg/kg)		
Number	50	50
Mean (SD)	1816.14 (917.21)	1830.35 (1078.36)
Geometric Mean (CV%)	1530.75 (50.503)	1495.44 (58.915)
Median	1866.70	1729.65
Q1 : Q3	1209.80 : 2287.50	1197.80 : 2206.70
Min : Max	71.5 : 5076.8	133.6 : 5410.7
GIR$_{max}$ (mg/kg/min)		
Number	50	50
Mean (SD)	2.82 (1.02)	2.93 (1.09)
Geometric Mean (CV%)	2.63 (36.019)	2.74 (37.044)
Median	2.75	2.70
Q1 : Q3	2.20 : 3.30	2.20 : 3.50
Min : Max	1.1 : 5.0	1.1 : 6.0
GIR-T$_{max}$ (h)		
Number	50	50
Mean (SD)	9.31 (7.78)	10.83 (9.07)
Median	9.85	11.54
Q1 : Q3	1.50 : 14.63	2.07 : 21.20
Min : Max	0.0 : 24.0	0.0 : 24.0

GIR = body weight standardized glucose infusion rate
GIRmax and GIR-Tmax are based on smoothed GIR profiles (LOESS, factor 0.06).
Q1 and Q3 denote first and third quartiles

None of the PD parameters were considered as primary; the main secondary PD parameter was the area under the body weight standardized glucose infusion rate (GIR) versus time curve from 0 to 24 hours after dosing on Day 6 (GIR AUC_{0-24}). The GIR AUC_{0-24} and the maximum glucose infusion rate (GIR_{max}) are equivalent for treatment T and R as shown for the treatment ratios with 90% CIs, indicating equivalent glucose disposal (see the table below).

Treatment ratio for GIR-AUC_{0-24} and GIR_{max} - pharmacodynamic population

Point estimates of treatment ratio with 90 % confidence intervals

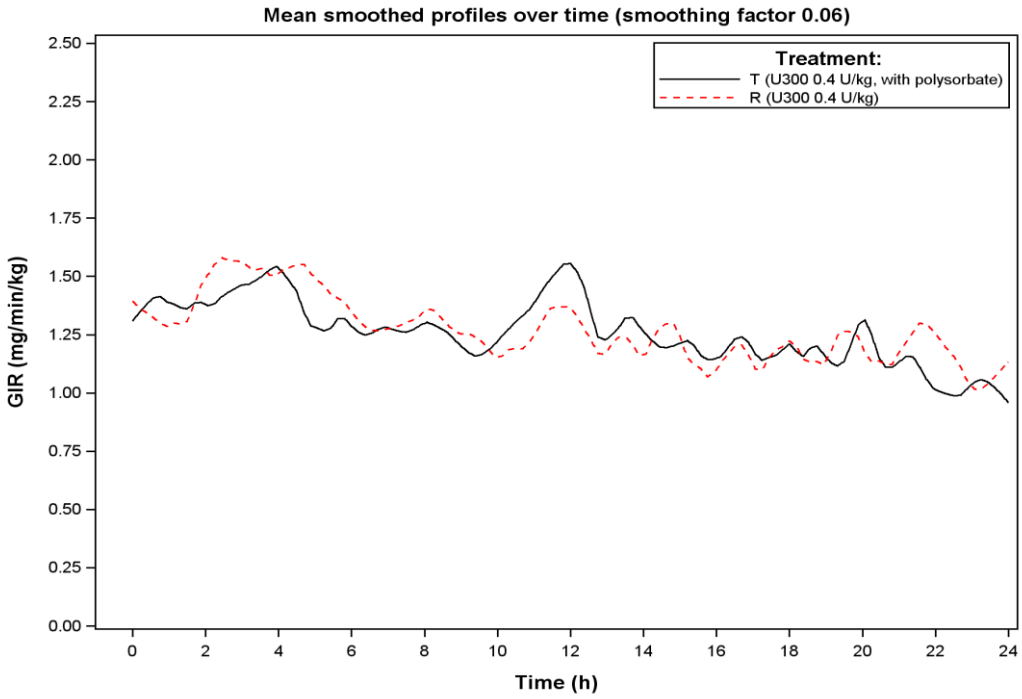
Treatment ratio	Parameter	Estimate	90% CI
T (U300 + polysorbate) / R (U300)	GIR-AUC_{0-24} [mg/kg]	1.02	(0.87 to 1.20)
	GIR_{max} [mg/kg/min]	0.96	(0.87 to 1.06)

GIR denotes body weight standardized glucose infusion rate

GIRmax is based on individually smoothed profiles, LOESS, factor 0.06.

Mean smoothed glucose infusion rate (GIR) profiles on Day 6 after multiple once daily dosing with treatment T or treatment R are presented in the figure below. The patterns of the 24-hour GIR profiles are comparable, and the glucodynamic activity is evenly balanced over the 24 hour period without a maximum.

Overlay plots of mean smoothed GIR over time



GIR = body weight standardized Glucose Infusion Rate

LOESS smoothing using factor = 0.06

Consistent with the evenly balanced GIR profiles, the $T_{50\%}$-GIR-AUC_{0-24} median values were 11.43 and 11.28 hours for treatment T and R, respectively (see the table below).

Descriptive statistics for $T_{50\%}$ of GIR-AUC_{0-24}

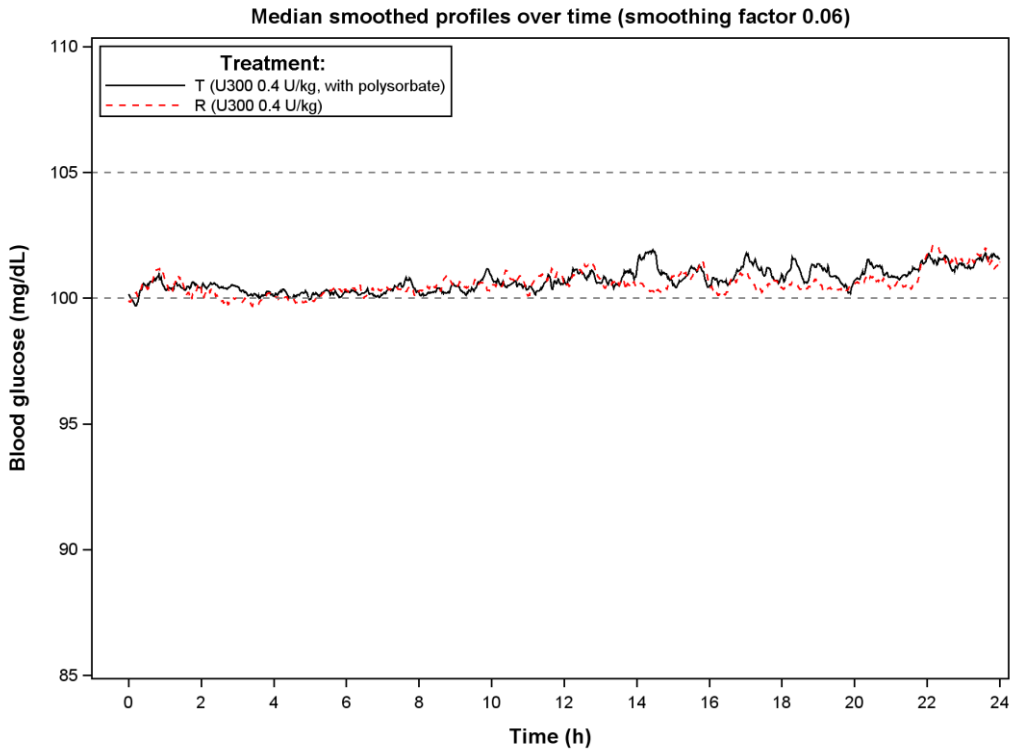
	T (U300 + polysorbate)	R (U300)
T50% GIR-AUC0-24h (h)		
Number	50	50
Mean (SD)	10.97 (2.79)	11.61 (3.42)
Median	11.43	11.28
Q1 : Q3	9.820 : 12.420	9.930 : 12.700
Min : Max	0.6 : 17.4	4.5 : 22.5

GIR = body weight standardized glucose infusion rate
Q1 and Q3 denote first and third quartiles

The time to 50% of GIR-AUC_{0-24} did not indicate any relevant differences between T and R, and the point estimate for the difference in $T_{50\%}$-GIR-AUC was -0.33 hours (90% CI: -1.04 to 0.38 hours). The time to 10%, 20%, and 90% of GIR-AUC_{0-24} did not indicate either any relevant differences between treatment T or R. The point estimate for the difference in GIR-T_{max} was -1.49 hours (90% CI: -4.87 to 1.50 hours).

The median smoothed blood glucose profiles were not different for T and R and stayed close to the targeted clamp level of 5.6 mmol/L (100 mg/dL), indicating tight blood glucose control for 24 hours regardless of treatment (see the figure below). During the clamp period of 24 hours, the median profiles were below the predefined euglycemic level of 5.8 mmol/L (105 mg/dL) for treatment T as well as for treatment R.

Overlay plots of median smoothed blood glucose over time



LOESS smoothing using factor = 0.06

Equivalent glucose disposal (bio-equipotency) was demonstrated for HOE901-U300 with polysorbate (treatment T) and without polysorbate (treatment R) as attested by 90% CIs for the treatment ratios T/R for GIR-AUC_{0-24} and GIR_{max} resting within the 0.80 to 1.25 acceptance range.

Safety results: Overall, both treatments were well tolerated with no relevant differences in any of the safety parameters.

TEAEs were reported in 18/50 subjects on treatment T and 15/50 on treatment R. No serious TEAEs were reported during the study, and no subjects discontinued treatment due to a TEAE. The most frequently reported TEAE was headache, reported in 10 subjects under treatment T and in 11 subjects under treatment R, followed by phlebitis (4 subjects under T), nausea (3 subjects under T and 1 subject under R) and presyncope (2 subjects under R).

One female subject with negative urine pregnancy tests at Day 1 of each treatment period had a positive urine pregnancy test at the EOS visit that was confirmed via serum pregnancy test and ultrasonography. The pregnancy is still ongoing at the time of reporting.

Overall, the percentages of subjects affected by treatment-emergent hypoglycemic events were comparable between treatment T (96%) and the R (94%), as well as the number of events per subject under the 2 treatments (T: 4.9; 243 episodes/ 50 evaluated subjects; R: 5.1; 254 episodes/50 evaluated subjects). There was 1 event of severe hypoglycemia, which occurred under treatment T. The event started about 2.5 hours after dosing on Day 2 in Period 1 during the in-house period. The subject received intravenous glucose and recovered immediately. The percentage of subjects with nocturnal hypoglycemia was comparable under treatment T (66.0%) and R (68.0%).

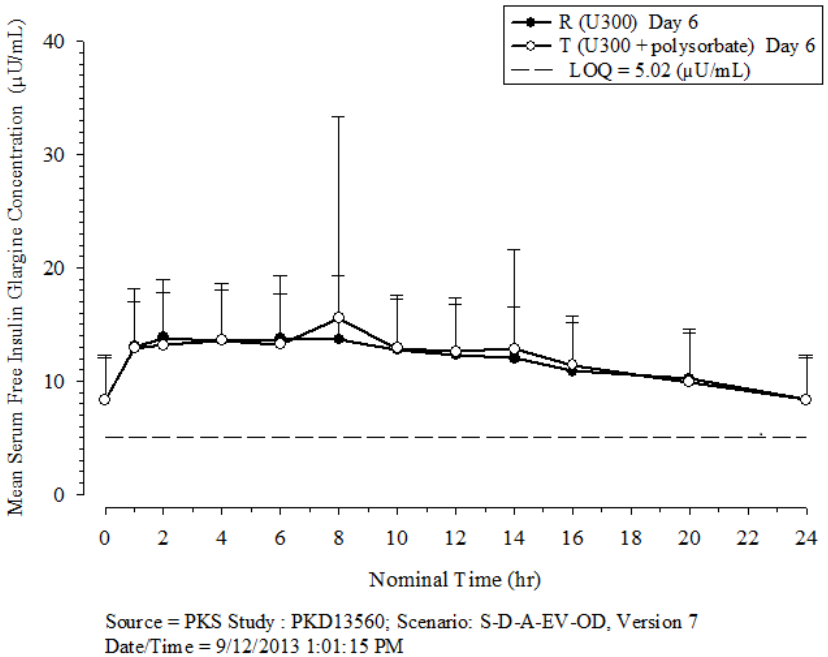
There were only few PCSA findings in clinical chemistry and vital signs, which were without clinical relevance and with no differences between treatments. There were few PCSAs for ECG parameters and without preference for either formulation. No ECG abnormalities were classified as clinically relevant by the Investigator.

A hardly perceptible erythema at the site of injection (Global Irritation Score=1, scale 0 to 5) was reported in 3 subjects under treatment T and 4 subjects under R. No further local reactions were observed for the 2 HOE901-U300 formulations.

The majority of the subjects (30/50) were negative for AIA and remained negative at the EOS visit, and, in further 4/50 negative cases, a conversion to positive occurred.

Pharmacokinetic results: In steady state, profiles of mean serum insulin glargine for treatment R and T displayed detectable exposure through 24 hours post dosing (see the figure below). The PK profiles were comparable for treatment R and T.

Mean (+SD) insulin glargine serum concentration time profiles at Day 6



Descriptive statistics of the main PK parameters for treatment T and R are provided in the 2 tables below. For 1 subject under treatment R, the PK parameters were not calculated as the serum concentrations could not be determined.

Pharmacokinetic data for insulin glargine by treatment

Mean ± SD (Geometric Mean) [CV%]	Free Insulin Glargine in Serum	
	T (U300 + polysorbate)	R (U300)
	Day 6	Day 6
N	50	49
INS-C_{max} [µU/ml]	18.6 ± 18.7 (15.8) [100.8]	16.6 ± 5.92 (15.6) [35.7]
INS-t_{max}[a] [h]	4.04 (1.00 - 16.00)	6.00 (1.00 - 24.00)
INS-AUC_{0-24} [µU•h/ml]	289 ± 107 (270) [36.9]	290 ± 93.5 (273) [32.3]

[a] Median (Min - Max)
Source = PKS Study : PKD13560; Scenario: S-D-A-EV-OD, Version 7

Pharmacokinetic data for insulin glargine by treatment ($T_{50\%}$ of INS-AUC_{0-24})

	T (U300 + polysorbate)	R (U300)
T50%-AUC0-24h (h)		
Number	50	49
Mean (SD)	10.805 (0.934)	10.682 (0.895)
Median	10.815	10.670
Q1 : Q3	10.530 : 11.380	10.390 : 11.230
Min : Max	8.05 : 12.59	7.72 : 12.84

Equivalence in bioavailability (bioequivalence) was demonstrated for HOE901-U300 with polysorbate (treatment T) and without polysorbate (treatment R) as attested by 90% CIs for the treatment ratios T/R for INS-AUC_{0-24} and INS-C_{max} resting within the 0.80 to 1.25 acceptance range.

Treatment ratio for INS-AUC_{0-24} and INS-C_{max} with 90% confidence intervals

Treatment ratio	Parameter	Estimate	90% CI
T (U300 + polysorbate) / R (U300)	INS-AUC0-24 (µU.h/mL)	1.00	(0.95 to 1.06)
	INS-Cmax (µU/mL)	1.02	(0.91 to 1.14)

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