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Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glargine (HOE901)	**Study Identifiers:** NCT01195454, EudraCT 2010-020914-27 **Study code:** PKD11627

Title of the study: A randomized, 4-sequence, cross-over, double-blind, dose response study of 0.4, 0.6 and 0.9 U/kg Insulin Glargine U300 compared to 0.4 U/kg Lantus® U100 in patients with diabetes mellitus type 1 using the euglycemic clamp technique

Study center(s): 1 center in Germany

Study period:

Date first patient enrolled: 23 August 2010

Date last patient completed: 09 December 2010

Phase of development: Exploratory (Phase 1)

Objectives:

Primary

To assess the metabolic effect ratios of three different insulin glargine U300 doses versus 0.4 U/kg Lantus® U100.

Secondary

To assess the exposure ratios of three different insulin glargine U300 doses versus 0.4 U/kg Lantus® U100, to compare the duration of action of different insulin glargine U300 doses versus 0.4 U/kg Lantus® U100, to explore the dose response and dose exposure relationship of insulin glargine U300, and to asses the safety and tolerability of insulin glargine U300 in patients with type 1 diabetes.

Methodology: Single-center, randomized, double-blind, cross-over (4 treatments, 4 treatment periods, and 4 sequences), single-dose (insulin glargine U300 formulation 0.4, 0.6, and 0.9 U/kg), active control (Lantus® U100 0.4 U/kg), in patients with type 1 diabetes mellitus (T1DM), using a euglycemic clamp technique

Number of patients:
Planned: 24
Randomized: 24
Treated: 24

Evaluated:
Pharmacodynamics: 22
Safety: 24
Pharmacokinetics: 22

Diagnosis and criteria for inclusion: Male and female patients with T1DM, aged 18 to 65 years old

Study treatments

Investigational product (T [Test]): Insulin glargine 300 U/mL solution for injection (insulin glargine U300)

Dose: Single dose injection of 0.4 (T_1), 0.6 (T_2), and 0.9 U/kg (T_3) insulin glargine U300
Administration: Subcutaneous (SC) administration at a periumbilical site of the abdomen, under fasting conditions

Reference therapy (R [Reference]): Insulin glargine 100 U/mL solution for injection (Lantus® U100, commercially available)

Dose: Single dose injection of 0.4 U/kg Lantus® U100
Administration: SC administration at a periumbilical site of the abdomen, under fasting conditions

Duration of treatment: 4 single administrations of T (insulin glargine 300 U/mL) or R (insulin glargine 100 U/mL) on Day (D)1 of treatment period (TP) 1 to 4, each administration followed by a 36-hour euglycemic clamp

Duration of observation: 4 - 11 weeks, depending on washout period and excluding screening (4 TPs of 2 days; 3 washouts of 5 - 18 days; end-of-study [EOS] visit between D5 and D14 after last study drug administration)

Criteria for evaluation:

Pharmacodynamics:

Primary: Area under the body-weight-standardized glucose infusion rate time curve between dosing and 36 hours after dosing (clamp end) (GIR-AUC_{0-36} [mg/kg]).

Secondary:

• Time (h) to 50% of GIR- AUC_{0-36} (T50%-GIR- AUC_{0-36} [hours]);

• Maximum smoothed body-weight-standardized glucose infusion rate (GIRmax [mg*min/kg]);

• First time after dosing to reach GIRmax (GIR-Tmax [hours]);

• Duration of euglycemia (time to elevation of smoothed blood glucose profile above clamp level of 100 mg/dL) calculated as the time from dosing to the last value of the smoothed blood glucose concentration curve at or below the level of euglycemia predefined as 105 mg/dL;

• Duration of controlled blood glucose within predefined margins defined as the time from dosing to the last value of the smoothed blood glucose concentration curve at or below 110, 130, and 150 mg/dL.

Additional:

Area under the body-weight-standardized glucose infusion rate time curve between dosing and time 24 hours (GIR- AUC_{0-24} [mg/kg]).

Safety: Adverse events (AEs) reported by the patient or noted by the Investigator, 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: Pharmacokinetic (PK) parameters for insulin glargine concentrations, calculated using non-compartmental methods: area under the concentration versus time curve from time zero to 24 and 36 hours post dosing (AUC_{0-24}, AUC_{0-36}), time to 50% of INS- AUC_{0-36} (T50%-INS- AUC_{0-36}), maximum concentration observed (INS-Cmax), and first time to reach INS-Cmax (INS-Tmax).

Pharmacokinetic sampling times and bioanalytical methods: Blood was collected for the determination of insulin glargine concentrations in serum at time points 0H, 1H, 2H, 4H, 6H, 8H, 12H, 16H, 20H, 24H, 28H, 32H, and 36H after injection of study medication in all treatment periods.

Insulin glargine (free form) in serum was determined using a radioimmunoassay with a lower limit of quantification (LOQ) of 5.02 µU/mL.

Statistical methods: Statistical analyses compared reference treatment (R) and test treatments (T1, T2, and T3).

Pharmacodynamics: Pharmacodynamic (PD) parameters were summarized by treatment using descriptive statistics. For GIR-AUC_{0-36}, the ratios of test (T1 to T3) and reference treatments (R) were assessed using a linear effects model for log transformed data. Estimate and 90% confidence interval (CI) for the treatment ratios of geometric means between T and R were provided for GIR- AUC_{0-36}. Time to 50% of GIR- AUC_{0-36} were compared non-parametrically between T (T1 to T3) and R. GIR- AUC_{0-36}, GIRmax, and GIR-Tmax were subject to corresponding analyses albeit supplemental parameters. The analyses were conducted on the PD population (all patients without any major deviations related to study drug administration, and for whom PD parameters were available).

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) and classified by system-organ classes (SOC) and preferred term (PT), were tabulated by treatment. All AEs were listed. For vital signs and ECG, frequencies of patients with abnormalities and potentially clinically significant abnormalities (PCSAs) were summarized by treatment. Frequencies for signs of local intolerance were analyzed by treatment. The analyses were conducted on the safety population (all patients who were exposed to any study treatment, regardless of the amount of treatment administered).

Pharmacokinetics: Pharmacokinetic (PK) parameters were summarized by treatment using descriptive statistics. For INS-AUC_{0-36}, the exposure of T (T1 to T3) and R was assessed using a linear effects model for log transformed data. Estimate and 90% confidence interval (CI) for the treatment ratios of geometric means between T and R were provided for INS- AUC_{0-36}. Time to 50% of INS- AUC_{0-36} (T50%-INS- AUC_{0-36}) were compared non-parametrically between T and R. The analyses were conducted on the PK population (all patients without any major deviations related to study drug administration, and for whom PK parameters were available).

Summary:

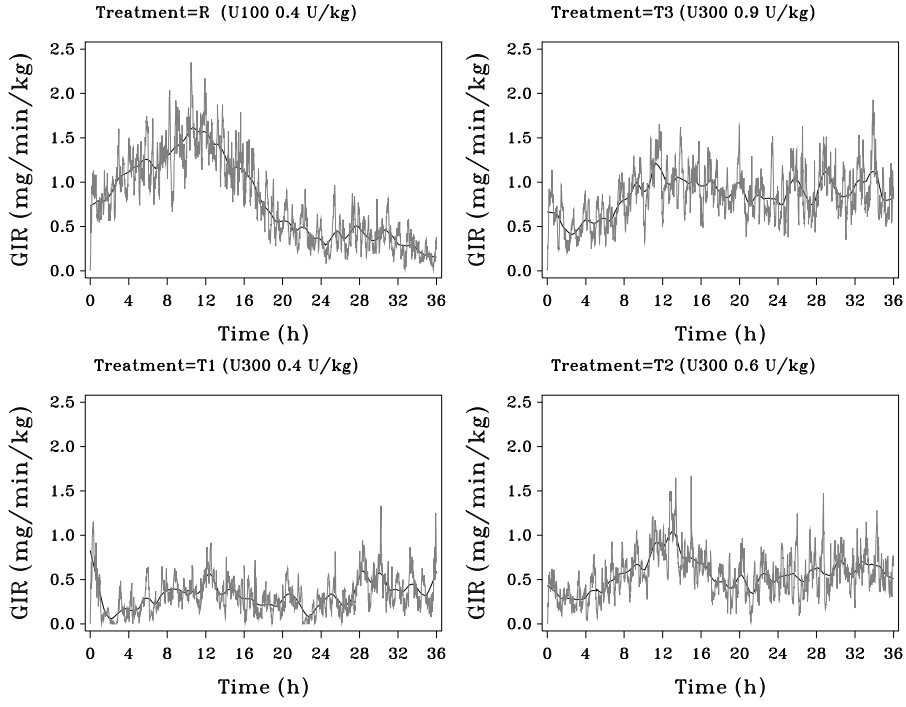
Pharmacodynamics results:

Mean smoothed body-weight-standardized glucose infusion rates (GIR) for insulin glargine U300 treatments (T1 to T3) were dose-dependent, with GIR profiles having a similar shape over the 36 hours clamp observation period after dosing (see the figure below).

Glucose infusion rates T1 to T3 gained from T2H onwards to level at around T12H. Thereafter GIR T1 to T3 slightly declined but eventually remained fairly stable up to the end of the clamp.

The R (Lantus U100) GIR profile, by contrast, presented a GIR gain without delay till the maximum at T12H and thereafter a constant decline towards T36H, in line with a characteristic end-of-dose-phenomenon of Lantus.

Body weight standardized glucose infusion rate (GIR) - Mean raw and mean smoothed profiles



GIR = body weight standardized Glucose Infusion Rate

R denotes injection of 0.4 U/kg Lantus® U100. T1, T2, and T3 denote injections of insulin glargine U300 (0.4, 0.6, and 0.9 U/kg respectively).

Total exogenous glucose consumption, GIR- AUC_{0-36}, increased with U300 doses. Compared to R, GIR- AUC_{0-36} was less under T1 and T2, but greater under T3 (see the table below).

Consistent with these findings, the T50%-GIR-AUC0-36 median values were around 18 (17 to 19) hours for T1 to T3, but 12 hours for R (see the table below).

Point estimates for GIR- AUC_{0-36} ratios (90%CI) are: T1/R 0.12 (0.05 to 0.30), T2/R 0.33 (0.17 to 0.66) and T3/R 1.37 (0.89 to 2.13). In particular under T1, several GIR profiles showed very low or even zero infusion rates. This affected normality assumptions for the statistical model and interpretability of estimated treatment ratios is limited.

PD parameters - based on body weight standardized glucose infusion rate (GIR)

		Test treatment		
	R (U100 0.4 U/kg)	**T1 (U300 0.4 U/kg)**	**T2 (U300 0.6 U/kg)**	**T3 (U300 0.9 U/kg)**
GIR-AUC_{0-36} (mg/kg)				
Number	22	22	22	22
Geometric Mean	1253.95	153.45	419.57	1691.03
CV%	53.330	93.424	91.106	41.467
Mean (SD)	1725.42 (920.16)	631.18 (589.67)	1117.65 (1018.25)	1844.58 (764.89)
Median	1672.30	411.10	926.20	1834.10
Min : Max	5.3 : 4255.8	1.0 : 1875.0	1.0 : 3877.7	762.0 : 3423.8
$T_{50\%}$-GIR-AUC_{0-36} (h)				
Number	22	18	21	22
Mean (SD)	11.84 (2.85)	16.71 (9.23)	17.70 (7.85)	19.84 (3.64)
Median	12.08	17.12	16.78	19.05
Min : Max	3.2 : 17.1	0.3 : 31.8	0.1 : 31.4	14.6 : 29.2

GIR = body weight standardized glucose infusion rate

R denotes injection of 0.4 U/kg Lantus® U100. T1, T2, and T3 denote injections of insulin glargine U300 (0.4, 0.6, and 0.9 U/kg respectively).

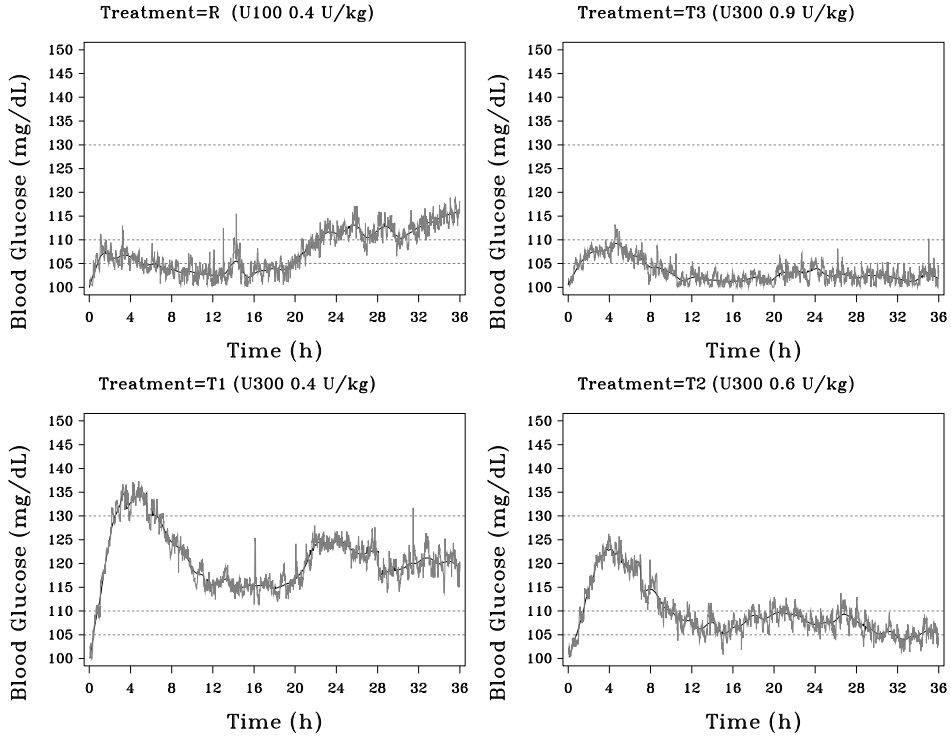
GIR-AUC values of zero were replaced by 1 mg/kg.

Similar to GIR, the shape of mean smoothed blood glucose (BG) profiles presented with compatible characteristics for all three test treatments T1 to T3. BG gained up to about T4H, then dropped until about T15H and remained fairly stable between T15H and T36H (end of clamp) (see the figure below).

Towards the end of clamp, mean smoothed T1 and T2 BG values were above clamp level (100 mg/dL) and the predefined level of euglycemia (105 mg/dL), but T2 BG was well within 105 - 110 mg/dL limits and T1 BG was within 110 - 130 mg/dL limits.

Mean smoothed BG profiles for T3 and R were similar until T20H with BG values between clamp level and predefined euglycemic level (100-105 mg/dL). After T20H, mean BG levels for R gradually increased to 115 mg/dl until clamp end, in line with the end-of-dose-phenomenon, while T3 BG remained within the clamp and euglycaemic level limits (100 – 105 mg/dL).

Blood glucose profiles over time - Mean raw and mean smoothed profiles



R denotes injection of 0.4 U/kg Lantus® U100. T1, T2, and T3 denote injections of insulin glargine U300 (0.4, 0.6, and 0.9 U/kg respectively).

Safety results:

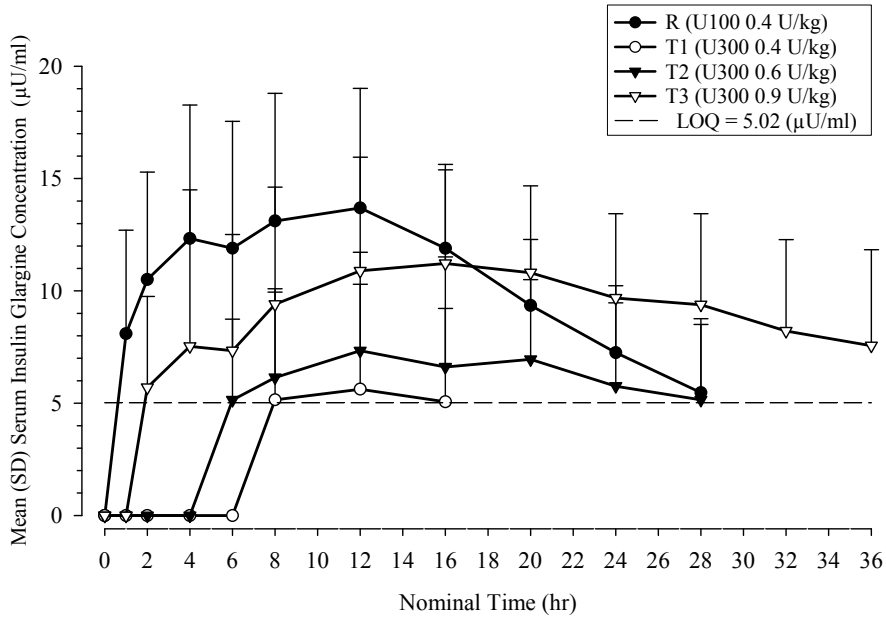
Two, 2 and 4 patients were reported to have a TEAE under R, T1, and T3, respectively. The most common TEAE was headache. One patient under T1 had an episode of ventricular extrasystoles after dosing with intensity rated by the investigator as severe but with no relationship to Investigational Product (IP) intake. There were no SAEs or withdrawals due to an AE. PSCAs occurred infrequently with no higher incidence for any treatment.

After administration of R, 2 patients developed a hardly perceptible erythema at the site of injection. No further local reactions were observed under T1, T2, and T3.

Pharmacokinetics results:

Mean serum insulin glargine concentrations versus time following a single SC dose of 0.4 U/kg Lantus U100 (R), 0.4 U/kg insulin glargine U300 (T1), 0.6 U/kg insulin glargine U300 (T2) and 0.9 U/kg insulin glargine U300 (T3) are presented in the figure below. Pharmacokinetic profiles for insulin glargine U300 treatments (T1 to T3) were flat between 8 and 16 hours, 6 and 28 hours, and over the 36 hours observation period for the U300 doses 0.4 U/kg (T1), 0.6 U/kg (T2), and 0.9 U/kg (T3), respectively. Following injection of 0.4 U/kg Lantus U100 (R), mean serum concentrations increased until 12 hours and declined afterwards with detectable concentrations up to 28 hours post dose. Overall, the profile of insulin glargine U300 doses (T1 to T3) showed flatter characteristics compared to Lantus U100 injections (R).

Mean (+SD) serum insulin glargine concentration time profiles (linear scale)



Source = PKS Study : PKD11627; Scenario: S-D-A-EV-OD, Version 1

The time to reach 50% of exposure (T50%-INS- AUC_{0-36}) was longer for patients receiving SC insulin glargine U300 doses (T1, T2, T3) compared to 0.4 U/kg Lantus U100 (see the table below). The median was 13 hours for treatment R whereas it was 15, 17, and 19 hours for T1, T2, and T3, respectively.

Mean ± SD T50%-INS- AUC_{0-36} of Lantus U100 0.4 U/kg and insulin glargine U300 0.4 U/kg, 0.6 U/kg and 0.9 U/kg

		Test treatment		
	R (U100 0.4 U/kg)	**T1 (U300 0.4 U/kg)**	**T2 (U300 0.6 U/kg)**	**T3 (U300 0.9 U/kg)**
T50%-AUC(0-36h) (h)				
Number	22	15	20	22
Mean (SD)	13.514 (2.212)	15.756 (4.839)	16.485 (5.648)	18.529 (2.064)
Median	13.460	14.950	16.580	18.570
Min : Max	8.53 : 17.44	6.63 : 25.32	2.27 : 26.19	15.62 : 23.53

AUC = Area under the insulin glargine concentration versus time curve
R denotes injection of 0.4 U/kg Lantus® U100. T1, T2, and T3 denote injections of insulin glargine U300 (0.4, 0.6, and 0.9 U/kg respectively).

The systemic mean exposure (INS- AUC_{0-36}) for U300 treatments increased with doses from 195, 206 up to 327 µU/mL for 0.4 U/kg, 0.6 U/kg, and 0.9 U/kg, respectively, in comparison to 318 µU/mL for Lantus U100 0.4 U/kg.

For insulin glargine U300 doses, the mean serum INS-Cmax of 0.4 U/kg (T1) and U300 0.6 U/kg (T2) were about 9 µU/mL (8.94 and 9.26 µU/mL, respectively), while INS-Cmax for insulin glargine U300 0.9 U/kg (T3) was 13.0 µU/mL. The highest INS-Cmax of 15.3 µU/mL was observed for Lantus U100 0.4 U/kg.

Individual INS-Tmax ranged up to 36 hours post dose for T1 to T3, but only up to 16 hours post dose for R.

Mean ± SD PK parameters of Lantus U100 0.4 U/kg, insulin glargine U300 0.4 U/kg, 0.6 U/kg and 0.9 U/kg

Mean ± SD (geometric mean) [CV%]	**Serum insulin glargine**			
	R (U100 0.4 U/kg)	**T1 (U300 0.4 U/kg)**	**T2 (U300 0.6 U/kg)**	**T3 (U300 0.9 U/kg)**
N[b]	22	15[c]	20[d]	22
INS-C_{max}	15.3 ± 5.95	8.94 ± 2.89	9.26 ± 2.79	13.0 ± 6.16
(µU/ml)	(14.2) [38.9]	(8.57) [32.3]	(8.87) [30.2]	(11.8) [47.2]
INS-T_{max} [a]	12.00	12.00	12.00	16.00
(hr)	(2.00 - 16.00)	(1.00 - 36.00)	(1.00 - 36.00)	(4.00 - 36.00)
INS-AUC_{0-36}	318 ± 109	195 ± 89.1	206 ± 105	327 ± 139
(µU•hr/ml)	(280) [34.3]	(177) [45.6]	(166) [51.0]	(288) [42.6]
INS-AUC_{0-24}	266 ± 92.3	148 ± 63.5	149 ± 76.1	222 ± 98.5
(µU•hr/ml)	(236) [34.7]	(136) [42.9]	(119) [51.0]	(196) [44.4]

[a] Median (Min - Max)

[b] Subjects 3 and 13 excluded from PK population (study discontinuation in period 1).

[c] Subject 23 not included in PK analysis in period 3 and 4 (unreasonable insulin glargine concentrations not matching to PD response). For subjects 4, 8, 11, 12, 20 and 22 all samples were below LOQ and PK parameters were not calculated.

[d] Subject 23 not included in PK analysis in period 3 and 4 (unreasonable insulin glargine concentrations not matching to PD response). For subject 22 all samples were below LOQ and PK parameters were not calculated.

Source = PKS Study : PKD11627; Scenario: S-D-A-EV-OD, Version 1
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Under T1, the dose-exposure (INS-AUC, INS-Cmax) could not be calculated in 6 out of 21 patients due to values below LOQ; these data were excluded from the summary statistics. This limits the interpretability of estimated treatment ratios with T1.

The point estimates for INS- AUC_{0-24} (90%CI) were 0.59 for the comparison T1/R, 0.49 for T2/R, and 0.84 for T3/R.

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