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 (insulin glargine)	**Study Identifiers:** NCT02201199, UTN U1111-1153-3712 & EudraCT 2014-001252-33 **Study code:** PDY13928
Title of the study: A single-center, randomized, double-blind, 3-treatment, 3-period, 6-sequence cross-over study to compare the pharmacokinetic and pharmacodynamic effects of single doses of insulin glargine given as U200 and U500 to Lantus® in a euglycemic clamp setting in subjects with type 1 diabetes	
Study center(s): 1 center in Germany	
Study period: Date first patient enrolled: 21/Aug/2014 Date last patient completed: 17/ Nov/2014, last contact on 01/Dec/2014	
Phase of development: Phase 1	
Objectives: Primary To compare the pharmacokinetic (PK) characteristics of single doses of insulin glargine given as U200 and U500 with those of a single dose of Lantus U100 in a euglycemic clamp setting in subjects with type 1 diabetes mellitus (T1DM). Secondary • To compare the pharmacodynamic (PD) characteristics of single doses of insulin glargine given as U200 and U500 with those of a single dose of Lantus U100 in a euglycemic clamp setting in subjects with type 1 diabetes. • To assess the safety and tolerability of single doses of insulin glargine given as U200, U500 and Lantus® U100 in subjects with type 1 diabetes under euglycemic clamp conditions.	
Methodology: This was a single-center, randomized, double-blind, cross-over (3 treatments, 3 treatment periods and 6 sequences), active control study. Single doses of 0.6 U/kg of insulin glargine were given as 3 different concentrations (U200 [T1], U500 [T2] and Lantus [U100] [R]) in a euglycemic clamp setting under fasting conditions. A wash-out period of 7 to 21 days separated consecutive dosing, ie, 4 to 18 days between each treatment period. The length of the wash-out period was individually variable allowing some operational flexibility.	
Number of patients**:** Planned: 36 Randomized: 36 Treated: 36 **Evaluated:** Pharmacodynamic: 36 Safety: 36 Pharmacokinetics: 36	

Diagnosis and criteria for inclusion: Male and female subjects aged between 18 and 65 years with type 1 diabetes mellitus for more than 1 year. Main inclusion criteria: total insulin dose of <1.2 U/kg/day; minimum usual basal insulin dose ≥0.2 U/kg/day; HbA_{1c} ≤9%; C-peptide <0.3nmol/L; body mass index (BMI) 18.5 – 30.0 kg/m^2.

Study treatments

Investigational medicinal product(s): Insulin glargine solution for injection: HOE901-U200, test treatment 1 (T1); HOE901-U500, test treatment 2 (T2); and Lantus U100, reference treatment (R).

Formulation:

- Insulin glargine 200 U/mL (U200) solution for injection as T1,
- Insulin glargine 500 U/mL (U500) solution for injection as T2,
- Insulin glargine 100 U/mL (Lantus U100) solution for injection as R.

Route(s) of administration: SC injection with an insulin syringe into a peri-umbilical site of the abdomen using a standardized skin-fold technique.

Dose regimen:

T1: Single dose of 0.6 U/kg insulin glargine U200.

T2: Single dose of 0.6 U/kg insulin glargine U500.

R: Single dose of 0.6 U/kg Lantus U100.

Noninvestigational medicinal product(s): Insulin glulisine was given as IV infusion during the euglycemic clamp procedure. Insulin glulisine and NPH insulin for SC administration was provided to the patients as needed for the transition period before the clamps. These insulin products were provided by the Investigator in their marketed form. Between the treatment periods, patients used their usual basal-bolus regimen.

Criteria for evaluation:

Pharmacodynamics:

None of the pharmacodynamic (PD) parameters were defined as primary.

Secondary endpoints:

Main secondary pharmacodynamic variable

- Area under the body weight standardized glucose infusion rate (GIR) versus time curve over 12 hours after investigational medicinal product (IMP) administration (GIR-AUC_{0-12}).

Further secondary pharmacodynamic variables

- Further time periods of the area under the body weight standardized GIR versus time curve were the first 24 hours and the full 36 hours after IMP administration (GIR-AUC_{0-24}, GIR-AUC_{0-36}) and additional fractional GIR-AUCs (GIR-AUC_{0-6}, GIR-AUC_{6-12}, GIR-AUC_{12-18}, GIR-AUC_{18-24}, GIR-AUC_{24-30}, GIR-AUC_{30-36});
- Time to reach at least 50% of the GIR-AUC within 36 hours ($t_{50\%}$-GIR-AUC_{0-36});
- Maximum smoothed body weight standardized GIR (GIR_{max}) and the time to GIR_{max}, GIR-t_{max};
- Times of controlled blood glucose (BG) within predefined margins from dosing to specified thresholds, ie, smoothed blood glucose levels at or below 5.8, 6.1, 7.2, 8.3 mmol/L (105, 110, 130 and 150 mg/dL)

Safety: Safety and tolerability of subjects was monitored via adverse events (AEs) spontaneously reported by the subjects or observed by the investigator throughout the study period; hypoglycemic episodes categorized based on the American Diabetes Association (ADA) classification. Safety was also assessed via clinical laboratory evaluations (hematology, coagulation test, biochemistry, serology, and urinalysis); vital sign measurements (HR, systolic blood pressure and diastolic blood pressure); electrocardiogram (ECG) recordings (standard 12-lead ECGs); measurements of serum anti-insulin antibodies (AIAs), body weight (kg); body temperature; physical examination; local tolerability at injection site; allergic or allergic-like reaction and symptomatic or asymptomatic overdose with IMP.

Pharmacokinetics:

Primary endpoints:

- Area under insulin glargine (INS) serum concentration versus time curve calculated using the non-compartmental methods from time zero to 12 hours post dosing (INS-AUC_{0-12}).

Secondary endpoints:

- INS-AUC_{0-24}, INS-AUC_{0-36}
- Time to 50% of INS-AUC_{0-36} ($t_{50\%}$ INS-AUC_{0-36})
- Area under the concentration versus time curve from time zero to the real time T_{last} (INS-AUC_{last}) and time corresponding to the last concentration above the limit of quantification Cl_{ast} (INS-tl_{ast});
- Maximum concentration observed (INS-C_{max}) and time to reach C_{max} (INS-t_{max});
- 6 hour fractions of INS- AUC_{0-36}.

Summary:

Population characteristics: 36 subjects with T1DM were randomized in the study. The mean age (range) was 43.6 years (21-64), 33 subjects were male and 3 female, and the mean BMI was 25.40 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:

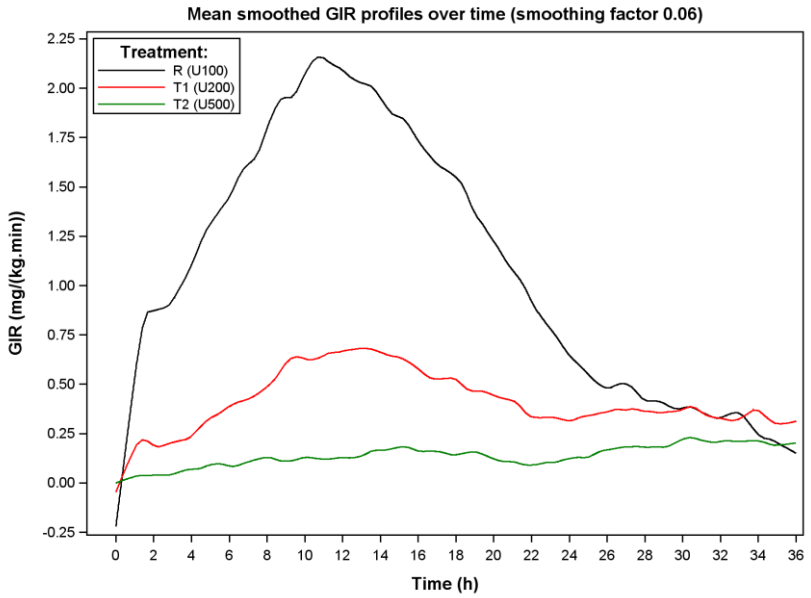
The glucose infusion rate (GIR) time profiles were different between the 3 formulations of 0.6 U/kg insulin glargine, with decreasing mean GIR-AUC_{0-12}, GIR-AUC_{0-24}, and GIR-AUC_{0-36}, as well as smoothed GIR_{max} with increasing concentration of the insulin glargine solution (100 U/mL [treatment R], 200 U/mL [treatment T1], 500 U/mL [treatment T2]) (Table 1, Figure 1). Under T2, 23 subjects had a GIR-AUC_{0-12} equal to 0 mg/kg and 13 subjects had a GIR-AUC_{0-36} equal to 0 mg/kg. Under T1, only 7 and 3 subjects had a GIR-AUC_{0-12} and a GIR-AUC_{0-36} of 0 mg/kg, respectively. Reference treatment R had only 1 subject with a GIR-AUC_{0-12} equal to 0 mg/kg. In particular for T2 (U500), these profiles showing zero infusion rates lead to a limited interpretability of estimated treatment ratios. The pairwise treatment comparisons of T1 versus R and T2 versus R revealed significant differences in the PD parameters GIR-AUC_{0-12}, GIR-AUC_{0-24}, GIR-AUC_{0-36} and GIR_{max} ($p<0.001$ for all parameters). For the treatment comparison T2 versus T1, the difference for these PD parameters was also statistically significant.

Under R (U100), the well described thorough and fast onset of activity was observed reaching a maximum at around 12 hours (GIR-t_{max}) (Table 1) and 50% of the overall metabolic activity ($t_{50\%}$-GIR-AUC_{0-36}) at around 14 hours after dosing. These time points occurred later under T1 (U200) with about 14 hours and 18.5 hours, respectively. The mean GIR profile of T1 (U200) showed a smoother onset of activity with an overall flatter profile This was in particular quantifiable with the lower mean GIR_{max} at 1.09 mg/kg/min under T1 (U200), whereas it was 2.53 mg/kg/min under treatment R (U100). After GIR-t_{max}, the GIR under R declined until around 24 hours and faded out further until 36 hours. In contrast, GIR under T1 (U200) only slightly decreased after GIR-t_{max}, reaching a plateau which was kept until clamp end (Figure 1).

The mean GIR profile of T2 (U500) was slightly above 0 all over the clamp duration with a slight increase until 12 hours after dosing and no downwards trend by end of clamp. The mean GIR-AUC_{0-12}, GIR-AUC_{0-24} and GIR-AUC_{0-36}, as well as smoothed GIR_{max} were all lower than with T1 (U200) and R (U100). GIR-t_{max} should be interpreted with caution for T2 (U500) as several values were equal to 0 (Q1=0) leading to a lower mean and median than in T1 (U200). $t_{50\%}$-GIR-AUC_{0-6} for T2 (U500) was reached at around 21.4 hours after dosing.

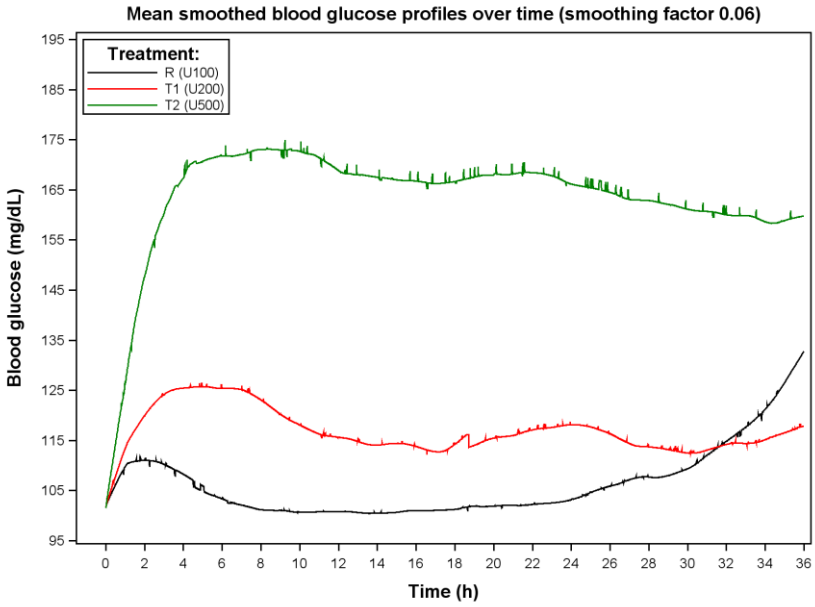
The mean GIR profiles of T1 and T2 did not return to 0 by end of clamp. Therefore a possible metabolic activity of these 2 treatments beyond 36 hours cannot be excluded.

Figure 1 - Overlay plots of mean smoothed GIR profiles over time



Smoothing factor: 0.06
R denotes injection of 0.6 U/kg Lantus® U100. T1 and T2 denote injections of insulin glargine 0.6 U/kg U200 respectively U500.
GIR = body weight standardized glucose infusion rate

Figure 2 - Overlay plots of mean smoothed blood glucose profiles over time



Smoothing factor: 0.06
R denotes injection of 0.6 U/kg Lantus® U100. T1 and T2 denote injections of insulin glargine 0.6 U/kg U200 respectively U500.
BG values after first administration
Note: In this graph smoothed BG values after rescue insulin are put to 250 mg/dL.

Table 1 - Descriptive statistics for GIR-AUC$_{0-12}$, GIR-AUC$_{0-24}$, GIR-AUC$_{0-36}$, GIR$_{max}$ and GIR-t$_{max}$

	R (U100)	T1 (U200)	T2 (U500)
GIR-AUC$_{0-12}$ (mg/kg)			
Number	36	36	36
Mean (SD)	1010.22 (563.25)	279.78 (315.31)	61.17 (140.73)
Median	1045.10	150.70	0.00
Q1 : Q3	498.10 : 1404.25	16.75 : 563.15	0.00 : 35.10
Min : Max	0.0 : 2192.7	0.0 : 1196.3	0.0 : 549.1
GIR-AUC$_{0-24}$ (mg/kg)			
Number	36	36	36
Mean (SD)	2060.54 (1161.77)	644.94 (700.04)	160.23 (311.91)
Median	1922.55	460.65	0.05
Q1 : Q3	1269.30 : 2777.05	86.75 : 932.00	0.00 : 149.65
Min : Max	70.5 : 4885.8	0.0 : 2793.1	0.0 : 1180.4
GIR-AUC$_{0-36}$ (mg/kg)			
Number	36	36	36
Mean (SD)	2338.20 (1248.55)	894.75 (844.60)	297.16 (454.29)
Median	2017.95	800.30	81.60
Q1 : Q3	1421.80 : 3103.70	220.10 : 1257.50	0.00 : 398.30
Min : Max	177.6 : 5055.5	0.0 : 3442.4	0.0 : 1781.2
GIR$_{max}$ (mg/(kg.min))			
Number	36	36	36
Mean (SD)	2.53 (1.24)	1.09 (0.71)	0.44 (0.46)
Median	2.34	0.92	0.42
Q1 : Q3	1.60 : 3.45	0.65 : 1.44	0.00 : 0.73
Min : Max	0.4 : 5.7	0.0 : 2.7	0.0 : 1.6
GIR-t$_{max}$ (h)			
Number	36	36	36
Mean (SD)	11.97 (4.46)	14.25 (10.07)	12.10 (13.83)
Median	11.25	12.95	5.92
Q1 : Q3	9.00 : 13.64	9.28 : 20.54	0.00 : 27.71
Min : Max	5.4 : 26.5	0.0 : 36.0	0.0 : 36.0

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
R denotes injection of 0.6 U/kg Lantus® U100. T1 and T2 denote injections of insulin glargine 0.6 U/kg U200 respectively U500.

Table 2 - Descriptive statistics for $t_{50\%}$-GIR-AUC_{0-36}

	R (U100)	T1 (U200)	T2 (U500)
$t_{50\%}$ of GIR-AUC_{0-36} (h)			
Number	36	33	23
Mean (SD)	14.11 (3.78)	18.53 (7.44)	21.39 (10.95)
Median	13.48	15.78	26.45
Q1 : Q3	11.93 : 15.49	14.18 : 23.42	15.25 : 30.25
Min : Max	8.6 : 28.8	1.6 : 35.1	0.0 : 34.1

GIR = body weight standardized glucose infusion rate
R denotes injection of 0.6 U/kg Lantus® U100. T1 and T2 denote injections of insulin glargine 0.6 U/kg U200 respectively U500.

The mean smoothed blood glucose profile under R (U100) indicated – after gaining full activity within 4-5 hours – a tight blood glucose control until around 24 hours (BG <105 mg/dL), followed by a gradual increase in BG as described previously for Lantus (end of dose phenomenon). The mean BG profile of treatment T1 (U200) needed with about 10 hours slightly longer until gaining full metabolic activity with stable BG control, which then remained nearly stable until end of clamp. The plateau level of the mean BG profile of T1 (U200) was at around 115 mg/dL and, thus, slightly higher than for R (U100). With a single dose of 0.6 U/kg T2 (U500) mean BG profiles reached a plateau from 4 to 10 hours after dosing at a level of around 170 mg/dL. After this plateau, the mean BG of T2 (U500) showed a permanent subtle downwards trend lasting until end of clamp where it reached about 160 mg/dL(Figure 2).

Descriptive statistics for BG control (Table 3) showed that the mean duration of euglycemia was slightly longer under R (U100) than with T1 (U200) (32.6h versus 31.3h, resp.), but the median of R (U100) was slightly shorter than for T1 (U200) (35.6h versus 36.0h). For T2 (U500), the mean duration of euglycemia was 19.9h, but with a rather high variability (SD 17.5h). The median under T2 (U500) was at 32.7h and the range was from 0.0 to 36.0h, indicating that for this formulation a single dose of 0.6 U/kg was too low to keep euglycemia for some patients, but for others already provided a tight BG control over more than 24 hours. Ten (10) patients under T2 (U500) received IV insulin infusion during the clamp ('rescue insulin'), whereas it was only 1 patient under T1 (U200) and none under R (U100).

Table 3 - Descriptive statistics for duration of controlled smoothed blood glucose (at or below 105/110/130/150 mg/dL) per treatment

	R (U100)	T1 (U200)	T2 (U500)
Controlled BG at or below 105 mg/dL (h)			
Number	36	34	33
Mean (SD)	32.566 (4.891)	31.299 (10.156)	19.927 (17.513)
Median	35.635	36.000	32.670
Min : Max	20.62 : 36.00	0.30 : 36.00	0.00 : 36.00
Controlled BG at or below 110 mg/dL (h)			
Number	36	36	34
Mean (SD)	33.225 (4.381)	31.267 (10.987)	19.511 (17.486)
Median	36.000	36.000	33.125
Min : Max	21.30 : 36.00	0.15 : 36.00	0.05 : 36.00
Controlled BG at or below 130 mg/dL (h)			
Number	36	36	36
Mean (SD)	34.016 (3.501)	32.091 (10.383)	19.866 (17.338)
Median	36.000	36.000	35.340
Min : Max	23.93 : 36.00	0.93 : 36.00	0.20 : 36.00
Controlled BG at or below 150 mg/dL (h)			
Number	36	36	36
Mean (SD)	34.822 (2.352)	33.286 (7.933)	22.060 (16.783)
Median	36.000	36.000	36.000
Min : Max	27.45 : 36.00	1.58 : 36.00	0.43 : 36.00

BG = Blood glucose (smoothed, LOESS factor 0.06)

R denotes injection of 0.6 U/kg Lantus® U100. T1 and T2 denote injections of insulin glargine 0.6 U/kg U200 respectively U500.

Safety results: Overall the treatment was well tolerated in all treatment groups. There were no deaths or serious treatment emergent adverse events reported in the study. No patients reported adverse events leading to discontinuation of study treatment. All reported treatment emergent adverse events (TEAEs) were mild or moderate in intensity.

The most frequently reported TEAEs were hypoglycemia events, reported in 6 patients under treatment R (U100) (16.7%), in 2 patients under T1 (U200) (5.6%) and in 3 patients under T2 (U500) (8.3%), all of which were classified as mild AEs. Two (2) patients under T2 (U500) had an orthostatic collapse (syncope) shortly after disconnection from the clamp setting in the night from Day 2 to Day 3. The event in Subject 020 was of moderate intensity and treated with an IV sodium chloride infusion. The other event in Subject 021 was classified as mild and did not require any treatment. Both events were classified as not drug-related by the investigator.

There were no TEAEs related to hypersensitivity reactions.

Other TEAEs categories were rare and similarly reported for all 3 treatment groups. These were in particular headache, nausea and vomiting.

Pharmacokinetic results: Mean serum concentration time profiles for insulin glargine R (U100) and T1 (U200) showed detectable exposure from 1 to 32 and 36 hours after dosing, respectively. The mean PK profile of T1 (U200) was flatter than the one for R (U100), with a mean Cmax of 12.6 µU/mL compared to 21.4 µU/mL, respectively. The mean concentration time profile of T2 (U500) was below lower limit of quantification (LLOQ, 5.02 µU/mL) for all time points (Figure 3).
In the T2 (U500) treatment group, 15 patients had all samples below LLOQ. This means that under T2, PK evaluation could not be performed in 15 out of 36 patients. Furthermore, 1 patient had 1 sample > LLOQ, and 3 patients had 2 samples > LLOQ. This overall limits the interpretability of systemic exposure as well as estimated treatment ratios with T2 (U500).

The systemic exposure over the first 12 hours of the clamp period (INS-AUC_{0-12}), as well as over the entire clamp period (INS-AUC_{0-36}), INS-AUC_{0-24} and INS-C_{max} decreased with increasing concentration of the formulation (Table 4). The reference treatment R (U100) showed the highest exposure, compared to treatment T1 (U200) and T2 (U500). Based on the limited data points above LLOQ for T2 (U500) accurate evaluation of partial AUCs could not be made for this treatment group.

The exposures expressed by INS-AUC_{0-12}, INS-AUC_{0-24}, INS-AUC_{0-36} and INS-C_{max} showed statistically significant differences for the comparisons of T1 (U200) versus R (U100), T2 (U500) versus R (U100), and T2 (U500) versus T1 (U200).

The time to reach 50% of INS-AUC_{0-36} (t50%-INS-AUC_{0-36}) increased with the concentration of the glargine formulation administered (Table 5).

Table 4 - PK parameters of serum insulin glargine

Mean ± SD (Geometric Mean) [CV%]	Serum insulin glargine		
	R (U100 0.6 U/kg)	T1 (U200 0.6 U/kg)	T2 (U500 0.6 U/kg)
N	36	35	21 *
INS-C_{max} (µU/mL)	21.4 ± 6.81 (20.3) [31.8]	12.6 ± 4.47 (11.8) [35.5]	9.18 ± 2.92 (8.77) [31.8]
INS-t_{max}[a] (h)	10.00 (1.00 - 16.00)	12.00 (2.00 - 28.00)	12.00 (1.00 - 36.00)
INS-AUC_{0-12} (µU•h/mL)	188 ± 64.7 (174) [34.3]	101 ± 44.3 (NA) [43.7]	55.3 ± 48.0 (NA) [86.8]
INS-AUC_{0-36} (µU•h/mL)	453 ± 137 (428) [30.4]	293 ± 124 (258) [42.2]	172 ± 112 (127) [65.2]

* 15 patients with all samples <LLOQ were excluded from this summary statistics
[a] median (min - max)

Table 5 - Descriptive statistics for $t_{50\%}$ -INS-AUC_{0-36}

	R (U100)	T1 (U200)	T2 (U500)
t50%-AUC_{0-36} (h)			
Number	36	35	21
Mean (SD)	14.154 (1.712)	15.926 (2.839)	16.584 (4.497)
Median	14.260	16.150	17.060
Q1 : Q3	12.800 : 15.320	14.910 : 17.590	14.830 : 18.720
Min : Max	10.76 : 17.85	8.08 : 22.02	3.01 : 25.75

R denotes injection of 0.6 U/kg Lantus® U100. T1 and T2 denote injections of insulin glargine 0.6 U/kg U200 respectively U500.

Figure 3 - Mean (+SD) serum insulin glargine concentration time profiles (linear-scale)

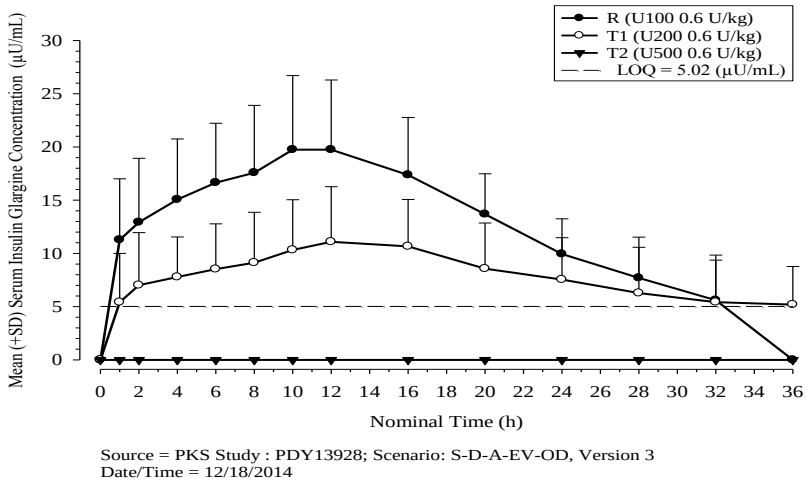


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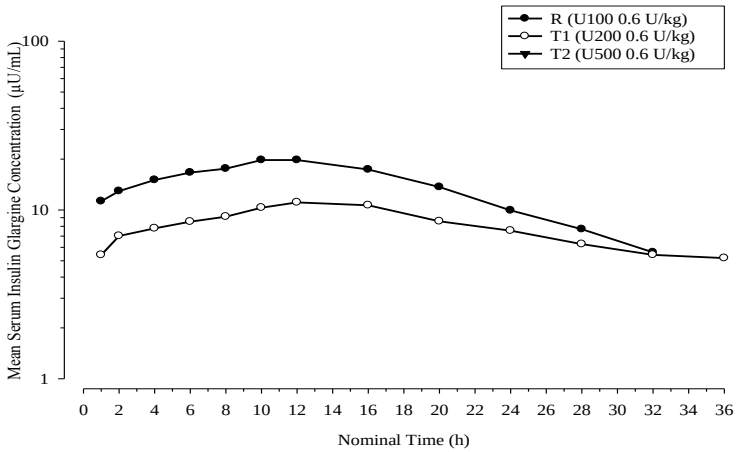
Figure 3 - Mean serum insulin glargine concentration time profiles (semi-log-scale)



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Date/Time = 12/18/2014

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