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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:** NCT01493115, U1111-1120-0463 **Study code:** PKD12270

Title of the study: A randomized, double-blind, 3-sequence, 3-period cross-over, single-dose study of a new formulation of insulin glargine compared to the marketed Lantus® in Japanese patients with type 1 diabetes mellitus using the euglycemic clamp technique

Study center: 1 site in Japan

Study period:

Date first patient enrolled: 11 November 2011

Date last patient completed: 07 April 2012

Phase of development: 1

Objectives:

- Primary objective:
  - To compare the metabolic effect of two different HOE901-U300 doses versus 0.4 U/kg Lantus®.
- Secondary objectives:
  - To compare the pharmacokinetic profile of two different HOE901-U300 doses versus 0.4 U/kg Lantus®
  - To compare the duration of action of different HOE901-U300 doses versus 0.4 U/kg Lantus®
  - To explore the dose response relationship of HOE901-U300
  - To explore the dose exposure relationship of HOE901-U300
  - To assess the safety and tolerability of HOE901-U300.

Methodology: Phase I, single-center, double-blind, randomized, crossover (3 treatments, 3 treatment periods and 3 sequences; Latin square), active control, single dose of insulin glargine (HOE901), 36-hour euglycemic glucose clamp, with 6-20 day wash-out duration between treatment periods

Number of patients**:** Planned: 18 (to have 15 patients for pharmacodynamic evaluation)

Randomized: 18

Treated: 18

Evaluated: Pharmacodynamics: 18

Safety: 18

Pharmacokinetics: 18

Diagnosis and criteria for inclusion: Japanese male or female patients, between 20 and 65 years of age, inclusive, with type 1 diabetes mellitus (T1DM) for more than one year, as defined by the Japanese Diabetes Society.

Study treatments

Investigational medicinal products: Insulin glargine

Formulation: Lantus® (U100): solution for injection containing 100 U/mL insulin glargine (marketed product)

HOE901-U300: solution for injection containing 300 U/mL insulin glargine (new formulation)

Route of administration: Subcutaneous administration into one peri-umbilical site of the abdomen under fasting conditions

Dose regimen: Reference (R): Single dose injection of 0.4 U/kg Lantus® (U100)

Test 1 (T_1): Single dose injection of 0.4 U/kg HOE901-U300

Test 2 (T_2): Single dose injection of 0.6 U/kg HOE901-U300

Non investigational medicinal products: Glucose solution, sodium chloride solution, heparin and insulin glulisine

Formulation:

- Glucose: 10% solution (Otsuka Pharmaceutical Co., Ltd.)
- Sodium chloride: 0.9% solution (Otsuka Pharmaceutical Co., Ltd.)
- Heparin sodium: 1000 U/mL saline (Mochida Pharmaceutical Co.,Ltd.)
- Apidra® (insulin glulisine): 100 U/mL solution (sanofi-aventis K.K.)

Route of administration: Intravenous bolus

Dose regimen:

- Glucose solution: Glucose solution will be infused with STG-22 (Nikkiso Co., Ltd., Japan) to keep subjects individual blood glucose at the determined target level.
- Sodium Chloride solution: Sodium chloride solution will be infused with STG-22 to keep the line patent for the glucose or Apidra® solution.
- Heparin Sodium: A low dose heparin solution (100 U/mL) will be infused with STG-22 via a double lumen catheter to prevent blood clotting in the BG measurement system [Heparin Sodium (100 U/mL): 50 000 U heparin sodium will be given to 500 mL saline solution.
- Apidra® (Insulin glulisine): Apidra® solution (0.4 U/mL) will be infused with STG-22 to achieve euglycemia [Apidra® (0.4 U/mL): 40 U Apidra® (0.4 mL) will be given to 97.6 mL of saline solution, to which 2 mL of the subject's own blood is added to prevent adhesion in the catheter].

Duration of treatment: Single dose (Day 1 of each period)

Duration of observation: Between 4 and 12 weeks (minimum-maximum duration, depending on wash-out period)

Criteria for evaluation:

Pharmacodynamics:

Primary: Area under the body weight standardized glucose infusion rate (GIR) versus time curve up to 36 h after dosing (GIR-AUC_{0-36})

Secondary:

- Time to 50% of GIR-AUC_{0-36} ($T_{50\%}$-GIR-AUC_{0-36})
- Maximum smoothed body weight standardized GIR (GIR_{max})

- Time to GIR_{max} ($GIR\text{-}T_{max}$)
- Duration from dosing to the last value of smoothed blood glucose (BG) concentration versus time curve at or below 105 mg/dL (Duration of euglycemia)
- Durations from dosing to the last value of smoothed BG concentration versus time curve at or below 110, 130 and 150 mg/dL (Duration of BG controlled)

Safety: Adverse events (AEs), electrocardiogram (ECG), vital signs, clinical laboratory, anti-insulin antibodies, local tolerability (subcutaneous injection site intolerances, if any)

Pharmacokinetics:

- Area under the insulin glargine concentration versus time curve from time zero to 36 hours post dosing ($INS\text{-}AUC_{0\text{-}36}$)
- Area under the insulin glargine concentration versus time curve from time zero to 24 hours post dosing ($INS\text{-}AUC_{0\text{-}24}$)
- Time to 50% of $INS\text{-}AUC_{0\text{-}36}$ ($T_{50\%}\text{-}INS\text{-}AUC_{0\text{-}36}$)
- Maximum insulin concentration ($INS\text{-}C_{max}$)
- Time to C_{max} ($INS\text{-}T_{max}$)

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Blood samples were collected for the determination of insulin glargine concentrations at time points 0H (predose), 1H, 2H, 4H, 6H, 8H, 12H, 16H, 20H, 24H, 28H, 32H and 36H after administration of IMP.

Serum concentrations of insulin glargine were determined using a validated radioimmunoassay (RIA) with a lower limit of quantification (LLOQ) of 5.02 µU/mL.

Plasma concentration of unchanged insulin glargine, and its metabolites M1 and M2 were determined using a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) with a LLOQ of 0.2 ng/mL.

Statistical methods:

Pharmacodynamics:

Pharmacodynamic parameters were summarized by treatment using descriptive statistics. Statistical analysis compared test (T_1 and T_2) with the reference (R) treatments. For log transformed $GIR\text{-}AUC_{0\text{-}36}$ and $GIR\text{-}AUC_{0\text{-}24}$, the ratios of test ($T_1$ and T_2) and reference (R) treatments were assessed using a linear mixed effects model. Estimate and 90% confidence interval (CI) for the treatment ratios of geometric means between test and reference treatments were provided for $GIR\text{-}AUC_{0\text{-}36}$ and $GIR\text{-}AUC_{0\text{-}24}$. $T_{50\%}\text{-}GIR\text{-}AUC_{0\text{-}36}$ and "duration of euglycemia" were compared non-parametrically between test (T_1 and T_2) and reference (R) treatments. GIR_{max}, $GIR\text{-}T_{max}$ and durations of blood glucose control were subject to corresponding analysis albeit a supplemental parameter.

Dose response relationship for HOE901-U300 doses was assessed.

Safety: The safety analysis was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics by treatment. For adverse events, frequencies of treatment-emergent adverse events (TEAEs) classified by MedDRA system organ class and preferred term were tabulated by treatment. All adverse events were listed.

For vital signs and ECG, frequency of patients with abnormalities and potentially clinically significant abnormalities (PCSAs) were summarized by treatment.

Pharmacokinetics:

Pharmacokinetic parameters were summarized by treatment using descriptive statistics. Statistical analyses compared test treatments (T_1 and T_2) against the reference treatment (R).

For log transformed INS-AUC_{0-36}, the exposure of test (T_1 and T_2) and reference (R) treatments were assessed using a linear mixed effects model. Estimate and 90% confidence interval (CI) for the treatment ratios of geometric means between test and reference treatments were provided for INS-AUC_{0-36}. $T_{50\%}$-INS-AUC_{0-36} was compared non-parametrically between test and reference treatments.

Dose exposure relationship for HOE901-U300 doses was assessed.

Summary:

Population characteristics:

Eighteen Japanese patients with T1DM were included and randomized in the study. No patient was prematurely withdrawn from the study and all randomized patients were included in the pharmacodynamic, pharmacokinetic and safety population.

Pharmacodynamic results:

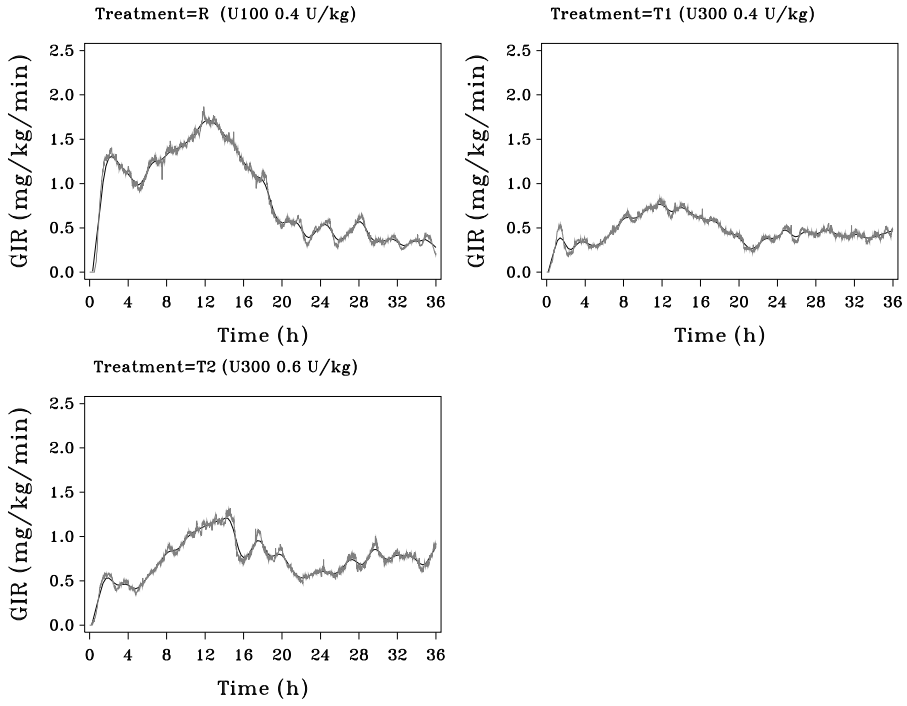
Mean and median smoothed glucose infusion rates (GIR) for the test treatments of HOE901-U300 (T_1 and T_2) gradually increased until approximately T12H, and thereafter slightly declined, and then remained fairly stable from approximately T24H until the end of the clamp at T36H.

The R (Lantus®) GIR profile, by contrast, was characterized by a rapid increase in GIR over the first hour, with a maximum GIR at around T12H, and thereafter declined.

Total exogenous glucose consumption, GIR-AUC_{0-36}, increased with increasing HOE901-U300 dose, but was lower compared to R. Point estimates for GIR-AUC_{0-36} ratios (90%CI) are: T_1/R 0.11 (0.04 to 0.33) and T_2/R 0.55 (0.36 to 0.84).

Consistent with the flatter time course for HOE901-U300 compared to Lantus®, the mean maximum GIR (GIR_{max}) was lower for the HOE901-U300 treatments, and the $T_{50\%}$-GIR-AUC_{0-36} median values were somewhat longer.

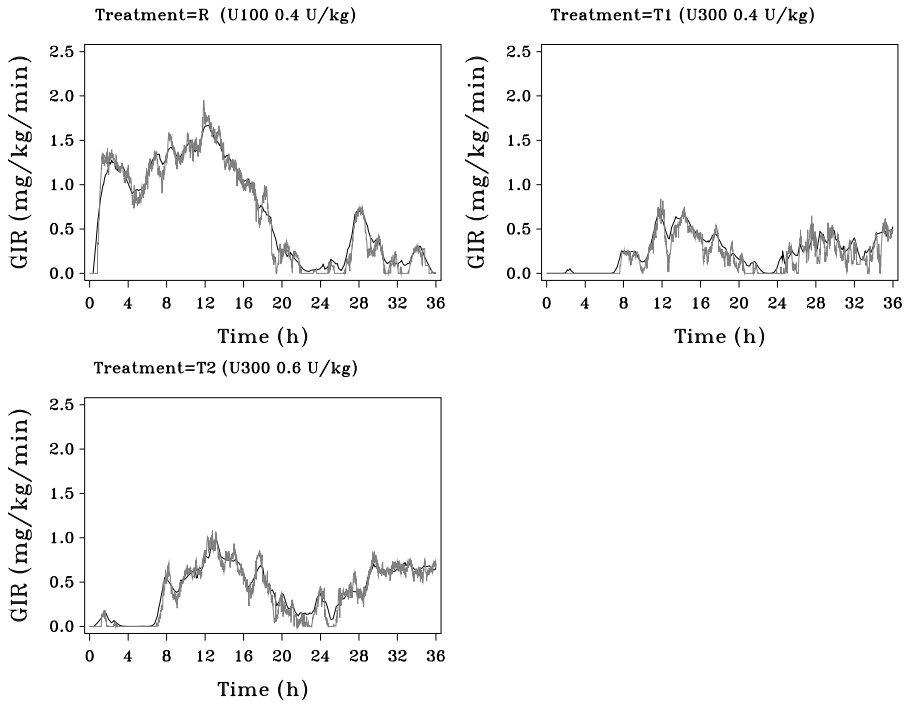
Body Weight standardized glucose infusion rate (GIR) – Mean raw and mean smoothed profiles



GIR = body weight standardized Glucose Infusion Rate. R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/pd_girmeanall_d_g.sas OUT=REPORT/OUTPUT/pd_girmeanall_d_g_i.rtf (29MAY2012 - 18:53)

Body weight standardized glucose infusion rate (GIR) - Median raw and median smoothed profiles



GIR = body weight standardized Glucose Infusion Rate

R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

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PD parameters of 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)**
GIR-AUC(0-24h) (mg/kg)			
Number	18	18	18
Geometric Mean	1304.18	84.11	245.85
CV%	58.445	138.146	117.506
Mean (SD)	1569.57 (917.34)	696.89 (962.72)	1068.53 (1255.59)
Median	1583.60	468.65	561.50
Min : Max	301.4 : 3720.2	0.0 : 4056.5	0.0 : 4430.3
GIR-AUC(0-36h) (mg/kg)			
Number	18	18	18
Geometric Mean	1525.33	173.87	841.78
CV%	58.375	124.496	108.038
Mean (SD)	1858.46 (1084.87)	990.30 (1232.88)	1590.89 (1718.76)
Median	1636.60	738.85	887.15
Min : Max	301.4 : 4460.6	0.0 : 5124.8	57.3 : 5753.1
GIR-AUC(12-36h) (mg/kg)			
Number	18	18	18
Geometric Mean	685.78	102.08	648.23
CV%	76.132	118.054	103.198
Mean (SD)	1003.61 (764.07)	663.83 (783.67)	1131.53 (1167.72)
Median	975.25	435.75	681.60
Min : Max	31.9 : 2876.7	0.0 : 3053.7	57.3 : 3831.8

GIR = body weight standardized glucose infusion rate

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

R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

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Estimates of treatment ratio with 90% confidence interval

Parameter	Comparison	Estimate	90% CI
GIR-AUC[0-36h]	T1 / R	0.11	(0.04 to 0.33)
	T2 / R	0.55	(0.36 to 0.84)
GIR-AUC[0-24h]	T1 / R	0.06	(0.02 to 0.22)
	T2 / R	0.19	(0.06 to 0.62)
GIRmax	T1 / R	0.14	(0.04 to 0.48)
	T2 / R	0.73	(0.60 to 0.90)

R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

GIRmax is based on smoothed GIR profiles.

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Maximum smoothed body weight standardized glucose infusion rate [GIRmax] - descriptive statistics

		Test treatment	
	R (U100 0.4 U/kg)	T1 (U300 0.4 U/kg)	T2 (U300 0.6 U/kg)
GIRmax (mg/kg/min)			
Number	18	18	18
Geometric Mean	2.03	0.29	1.48
CV%	37.643	81.989	72.219
Mean (SD)	2.16 (0.81)	1.23 (1.01)	1.83 (1.32)
Median	1.85	1.23	1.36
Min : Max	1.1 : 4.0	0.0 : 4.3	0.4 : 5.1

GIR = body weight standardized glucose infusion rate

GIRmax values of zero were replaced by 0.001 mg/kg/min.

R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

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PD parameter $T_{50\%}$-GIR-AUC_{0-36}

		Test treatment	
	R (U100 0.4 U/kg)	T1 (U300 0.4 U/kg)	T2 (U300 0.6 U/kg)
T50% GIR-AUC(0-36) (h)			
Number	18	14	18
Mean (SD)	12.37 (3.02)	18.03 (8.41)	20.43 (7.06)
Median	12.91	16.67	18.12
Min : Max	7.1 : 17.5	1.3 : 35.7	12.4 : 34.8

GIR = body weight standardized glucose infusion rate

n=14, Subject 392001001, 392001010, 392001011, 392001015 not included in calculation of summary statistics due to no glucose infusion in T1 (U300 0.4 U/kg).

R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

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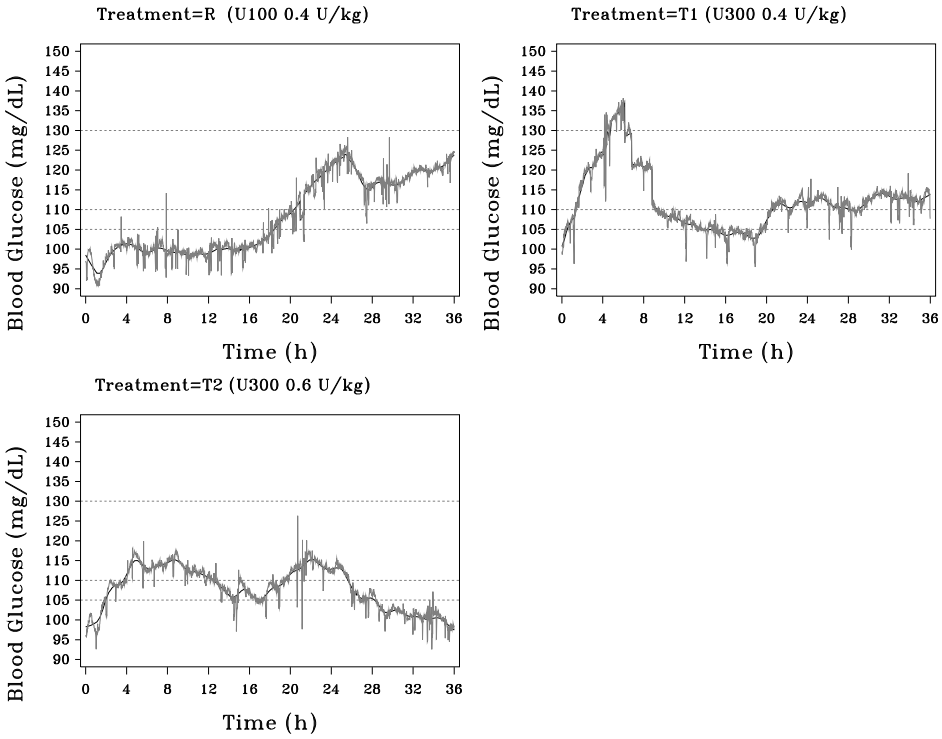
The shape of mean smoothed blood glucose (BG) profiles exhibited somewhat similar characteristics for the two test treatments, T_1 and T_2. Blood glucose increased up to about T6H, reflecting the time needed for T_1 and T_2 to take effect, with a larger increase observed following the low dose test treatment T_1. For both T_1 and T_2, blood glucose subsequently stabilized below the predefined glucose control threshold of 120 mg/dL throughout the duration of the clamp (36 hours). In contrast, for the treatment R, mean smoothed BG values were maintained below 120 mg/dL from the onset of clamp until T24H, but increased thereafter, consistent with a more rapid onset but less sustained time course of action.

The median BG profiles displayed generally similar characteristics although the values remained within a narrower range. As with the mean BG profiles, the median BG is lower for R than for T_1 and T_2 during the initial hours, but higher for R than for T_1 and T_2 beyond T16H, consistent with the slower onset but more sustained action of the test treatments T_1 and T_2.

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



R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).
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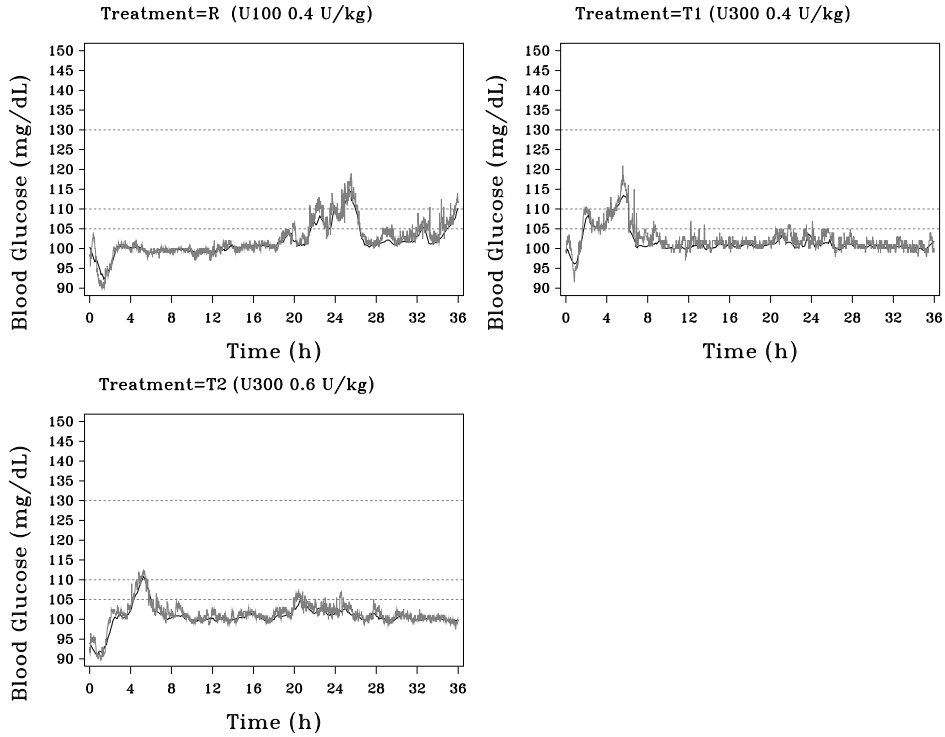
Blood glucose profiles over time – Median raw and median smoothed profiles



R denotes injection of 0.4 U/kg Lantus® U100. T1 and T2 denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

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Safety results:

There were no SAEs or withdrawals due to an AE. Treatment-emergent adverse events (TEAEs) were reported in 1 patient who had two episodes of hypoglycemia of mild intensity after treatment with R and T_1, respectively.

It was judged by the Investigator that these events were not related to the study medication, since the events occurred 2 or 3 days after the study medication and immediately after the patients' standard insulin treatment.

The PCSAs for laboratory parameters, vital signs or ECG parameters were observed infrequently, none of clinical significance and with no significant differences between HOE901-U300 and Lantus® treatment group.

The anti-insulin antibody status (positive, negative) did not change significantly: 15 (83.3%) positive outcomes at baseline and 14 (77.8%) positive outcomes at EOS.

Pharmacokinetic results:

Three patients (392001001, 392001010, and 392001015) having received T_1 (HOE901-U300 0.4 U/kg) did not show measurable insulin glargine exposure, which is in line with missing activity.

The mean concentration profiles of serum insulin glargine after single dose SC injection were without pronounced peak for all treatments, with the appearance of a somewhat flatter profile for the two test treatments.

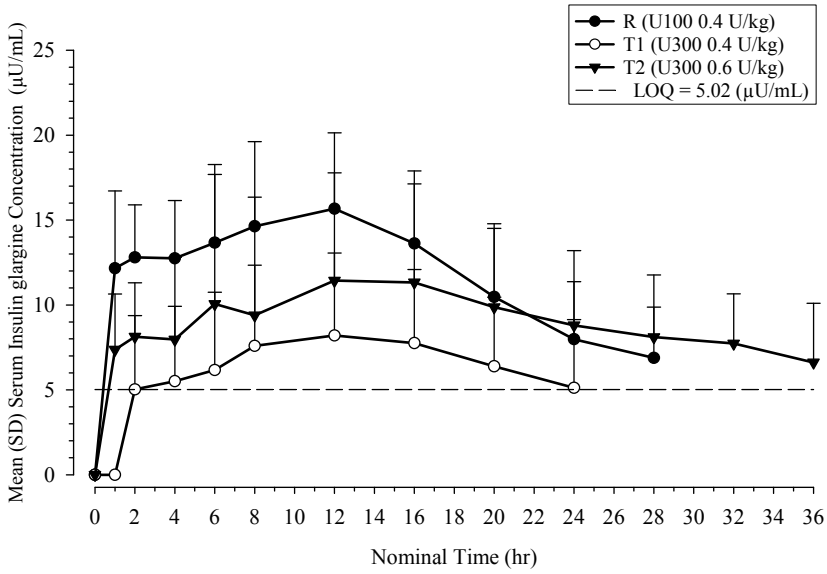
For treatment T_1 (HOE901-U300 0.4 U/kg), the mean serum concentration was above LLOQ from 2 to 24 hours, for treatment T_2 (HOE901-U300 0.6 U/kg) from 1 to 36 hours, and for the reference treatment R (Lantus® 0.4 U/kg) from 1 to 28 hours. Serum concentrations were more stable over the T12H to T24H for the test treatments compared to R, and for T_2 this was also evident between T24H and T36H. The maximum concentration, INS-C_{max}, was higher for Lantus® (R).

The exposures over 24 hours after injection (INS-AUC_{0-24}) as well as over the whole clamp period (INS-AUC_{0-36}) were higher under R than with T_1 and T_2, and increased with HOE901-U300 doses. The INS-T_{max} values were higher for the test treatments T_1 and T_2.

The point estimates of the treatment ratios for INS-AUC_{0-36} (90%CI) were: T_1/R 0.62 (0.51; 0.75) and T_2/R 0.75 (0.59; 0.94).

The apparently somewhat flatter profiles of T_1 and T_2 compared to R are also reflected in the times to reach 50% of the exposure over the whole clamp period ($T_{50\%}$-INS-AUC_{0-36}); the medians were about 17 and 18 hours for T_1 and T_2, respectively, and about 14 hours for R.

Mean (±SD) serum insulin glargine concentration time profiles



Source = PKS Study : PKD12270; Scenario: S-D-A-EV-OD, Version 4

PK parameters of serum insulin glargine

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)
N	18	15[b]	18
INS-C_{max} (µU/mL)	17.3 ± 4.75 (16.6) [27.5]	10.9 ± 3.39 (10.4) [31.2]	13.8 ± 7.08 (12.3) [51.5]
INS-T_{max}[a] (h)	8.00 (1.00 - 16.00)	16.00 (1.00 - 32.00)	14.00 (1.00 - 32.00)
INS-AUC_{0-24} (µU•h/mL)	303 ± 78.8 (291) [26.0]	190 ± 66.5 (176) [35.0]	232 ± 123 (NA) [52.9]
INS-AUC_{0-36} (µU•h/mL)	370 ± 101 (352) [27.2]	251 ± 91.6 (233) [36.4]	326 ± 156 (262) [47.8]

[a] Median (Min - Max) NA (not applicable)

Source = PKS Study : PKD12270; Scenario: S-D-A-EV-OD, Version 4

[b] Subject: 392001001, 392001010, 392001015 not included in calculation of summary statistics due to rescue insulin treatment in T1 (U300 0.4 U/kg)

Estimates of treatment ratio with 90% confidence interval

Parameter	Comparison	Estimate	90% CI
AUC[0-36h]	T1 / R	0.62	(0.51 to 0.75)
	T2 / R	0.75	(0.59 to 0.94)
AUC[0-24h]	T1 / R	0.58	(0.46 to 0.74)
	T2 / R	0.58	(0.38 to 0.86)
C_{max}	T1 / R	0.61	(0.52 to 0.73)
	T2 / R	0.74	(0.64 to 0.86)

R (reference treatment) denotes injection of 0.4 U/kg Lantus®U100.

T1 and T2 (test treatments) denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

LOQ values were set to zero for PK analysis.

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PK parameter $T_{50\%}$-INS-AUC_{0-36}

		Test treatment	
	R (U100 0.4 U/kg)	T1 (U300 0.4 U/kg)	T2 (U300 0.6 U/kg)
T50%-INS-AUC(0-36h) (h)			
Number	18	15	18
Mean (SD)	13.597 (2.140)	15.649 (3.113)	18.160 (3.858)
Median	14.420	16.590	17.505
Min : Max	8.16 : 16.12	9.86 : 20.23	13.27 : 32.00

AUC = Area under the insulin glargine concentration versus time curve

n=15, Subject 392001001, 392001010, 392001015 not included in calculation of summary statistics due to rescue insulin treatment in T1 (U300 0.4 U/kg).

R (reference treatment) denotes injection of 0.4 U/kg Lantus®U100.

T1 and T2 (test treatments) denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).

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