

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**206538Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## CLINICAL PHARMACOLOGY REVIEW

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| <b>NDA</b>                   | 206-538 Serials 0000, 0003                                |
| <b>Submission Dates</b>      | April 25, 2014, July 29, 2014                             |
| <b>Brand Name</b>            | TOUJEO  |
| <b>Generic Name</b>          | Insulin glargine  |
| <b>Reviewer</b>              | S.W. Johnny Lau, R.Ph., Ph.D.                             |
| <b>Team Leader (Acting)</b>  | Manoj Khurana, Ph.D.                                      |
| <b>OCP Division</b>          | Clinical Pharmacology 2                                   |
| <b>OND Division</b>          | Metabolism and Endocrinology Products                     |
| <b>Sponsor</b>               | sanofi-aventis U.S. LLC                                   |
| <b>Formulation; Strength</b> | Solution for injection; 300 U/mL                          |
| <b>Relevant IND</b>          | 112,400   |
| <b>Indication</b>            | Improve glycemic control in adults with diabetes mellitus |

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## 1 Executive Summary

The sponsor submitted NDA 206-538 to seek approval of HOE901-U300 (insulin glargine: 1800 nmol/mL or 300 U/mL) for the indication to improve glycemic control in adults with diabetes mellitus. HOE901-U300 has 3 times the amount of insulin glargine and zinc content (300 U/mL) than the approved Lantus (insulin glargine 100 U/mL: NDA 21-081 approved on April 20, 2000, sanofi-aventis). This document reviews the Clinical Pharmacology data of NDA 206-538. For simplicity, this review refers to HOE901-U300 as U300 and to Lantus as U100.

### 1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 206-538 Serials 0000 and 0003 and finds it acceptable. OCP recommends the following labeling actions:

#### **Labeling Action: Dosage and Administration and Clinical Pharmacology:**

- a. The pharmacokinetics/pharmacodynamics (PK/PD) comparison of U300 to Lantus demonstrates that the glucose lowering effect of U300 is lower than Lantus on a unit-to-unit basis.
- b. The PK/PD differences were consistent with the observed higher average basal insulin dose utilization in the efficacy/safety trials in both type 1 diabetes and type 2 diabetes patients. This information needs to be adequately conveyed to the prescribers of TOUJEO.
- c. **Therefore, OCP recommends the following action on the label:**

#### **2.3 Switching to TOUJEO from LANTUS (insulin glargine 100 Units/mL) or other insulin therapies**

Specify the following:

Patients switching from stabilized dose of basal insulin to TOUJEO may need higher daily unit dose of TOUJEO (see Clinical Pharmacology (12)).

#### **Under Clinical Pharmacology:**

##### **12.2 Pharmacodynamics**

Specify the following:

The glucose lowering effect of one unit of TOUJEO is lower (approximately 30% at steady state) than that from one unit of LANTUS. The difference in glucose lowering effect is consistent with, on average, higher TOUJEO unit dose utilization than LANTUS in the clinical trials.

### 1.2 Post Marketing Requirement

None.

### 1.3 Summary of Important Clinical Pharmacology Findings

In support of NDA 206-538, the sponsor submitted 6 clinical pharmacology studies to characterize and compare the pharmacokinetics/pharmacodynamics (PK/PD) characteristics, and 4 efficacy/safety studies to establish the non-inferiority of U300 in comparison to Lantus. The following are the key findings from a clinical pharmacology perspective:

- **Single Dose PK/PD:** For single subcutaneous administrations, the mean insulin glargine  $C_{max}$  was 8.9, 9.3, and 13.0  $\mu\text{U/mL}$ , respectively, and the mean insulin glargine  $\text{AUC}_{0-36}$  was 195, 206, and 327  $\mu\text{U}\cdot\text{hr/mL}$ , respectively, for the 0.4 U/kg, 0.6 U/kg, and 0.9 U/kg U300 doses, whereas the mean insulin glargine  $C_{max}$  was 15.3  $\mu\text{U/mL}$  and the mean insulin glargine  $\text{AUC}_{0-36}$  was 318  $\mu\text{U}\cdot\text{hr/mL}$  for the 0.4 U/kg U100 dose. The relative bioavailability (based on  $\text{AUC}_{0-36}$ ) of insulin glargine for the 0.4, 0.6, and 0.9 U/kg U300 doses was on average 63, 57, and 103%, respectively, as compared to that of the 0.4 U/kg U100 dose. Accordingly, in the euglycemic clamp, the overall glucose lowering effect (measured as rate of exogenously infused glucose over time to maintain

blood glucose at pre-specified clamp concentration; GIR-AUC<sub>0-36</sub>) was 12, 33, and 137%, respectively, as compared to that of the 0.4 U/kg U100 dose. On average, the GIR data indicates that onset of PD effect was slower (about 3 hours onwards), relatively flat, and extended beyond 24 hours for U300 than those of 0.4 U/kg U100. The pharmacokinetics of U300 is less than dose-proportional for single subcutaneous doses from 0.4 U/kg to 0.9 U/kg in T1DM patients. There appears to be a trend of increasing GIR-AUC<sub>0-36</sub> with U300 doses as the mean (SD) GIR-AUC<sub>0-36</sub> was 631.18 (589.67), 1117.65 (1018.25), 1844.58 (764.89) mg/kg, respectively, for 0.4 U/kg, 0.6 U/kg, and 0.9 U/kg U300.

- **Multiple Once-Daily Dose PK/PD:** The steady state serum insulin glargine concentration versus time profiles for treatments with 0.4 U/kg and 0.6 U/kg U300 were generally flat and showed detectable exposure and corresponding mean serum insulin glargine concentrations until 32 and 36 hours postdose, respectively. However, serum insulin glargine concentrations were quantifiable until 28 hours after SC administration of 0.4 U/kg U100. Treatment of 0.4 U/kg U300 produced lower pharmacodynamic response (GIR-AUC<sub>0-24</sub>) than that of 0.4 U/kg U100 in the euglycemic clamp. U300 reaches steady state in 5 – 7 days after daily 0.4 U/kg to 0.6 U/kg subcutaneous administrations in T1DM patients. At steady state, a trend for higher GIR-AUC<sub>0-24</sub> at higher insulin glargine AUC<sub>0-24</sub> was observable.
- **Implications of PK/PD Differences:** Collectively, single dose and steady state PK/PD data showed that the glucose-lowering effect of U300 is lower than U100 on a unit-to-unit basis over the proposed once-daily dosing interval. This difference in the overall glucose lowering effect on a unit-to-unit basis was consistent with the observed higher average basal insulin unit dose utilization of U300 than Lantus in the Phase 3 efficacy/safety trials in both type 1 diabetes and type 2 diabetes patients. Despite this observation, the efficacy/safety trials demonstrated the non-inferiority of U300 treatment to Lantus treatment (see Dr. Tania Condarco's Clinical Review in DARRTS for details). The treatment initiation algorithms and titration algorithms used in the trial protocols for transitioning patients to U300 treatment and the associated efficacy/safety comparison further supports the basis for labeling language on Dosing and Administration. Nonetheless, the PKPD data bring some important information on the time action profile of U300 that clinicians need to be aware when prescribing this product, namely the longer time to onset of action (approximately 6 hours) after 1<sup>st</sup> dose, longer time to reach steady-state (5 – 7 days) upon initiation and dose adjustment, prolonged action ( $\geq 24$  hours), and the need for higher unit doses of TOUJEO in patients stabilized on basal insulins upon change to U300. TOUJEO has inherent potential of downward drift in the systemic exposure and PD response for a unit dose of subcutaneously administered insulin (in reference to U100). Thus, TOUJEO may be unsuitable to be considered for molar dose ratio assessment/dose-response comparison in PK/PD studies for other insulin products.
- **Intra-subject Variability:** U300 PK and PD parameters show higher intra-subject variability than those of U100. For PK parameters, the intra-subject variability for INS-AUC<sub>0-24</sub> and INS-C<sub>max</sub> are 21% and 26%, respectively for U300, and 16% and 20%, respectively for U100. For PD parameters, the intra-subject variability for GIR-AUC<sub>0-24</sub> and GIR<sub>max</sub> are 40% and 41%, respectively for U300, and 20% and 26%, respectively for U100.

(b) (4)

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S.W. Johnny Lau, R.Ph., Ph.D.  
OCP/DCP2

FT signed by Manoj Khurana, Ph.D., Team Leader (Acting), \_\_\_\_\_ 1/ /15

An Office Level Clinical Pharmacology Briefing for NDA 206-538 was conducted on December 8, 2014; participants included D. Abernethy, V. Sinha, N. Mehrotra, I. Zadezensky, T. Condarco, R. Whitehead, C. Sahajwalla, S. Doddapaneni, M. Khurana, and J. Lau in person; L. Yanoff via phone.

## 2 Question-Based Review

The following is the background information on the clinical pharmacology of insulin glargine and U300 besides the Lantus product labeling:

- Hilgenfeld et al. *Drugs* 2014;74:911-27
- Sutton et al., *Expert Opin Biol Ther* 2014;14:1849-60

See Drs. Sam Haidar and Michael Fossler’s Clinical Pharmacology Review for Lantus in DARRTS (NDA 21-081’s Action Package dated September 19, 2005 on Pages 650 – 722/1166).

### 2.1 General Attributes

#### 2.1.1 What is the formulation of the to-be-marketed U300 and how does it differ from the commercialized Lantus formulation for subcutaneous (SC) administration?

The sponsor seeks approval to market the U300 cartridge formulation for SC administration. This U300 formulation has the same composition as the commercialized Lantus formulation (U100) except it has 3 times the amount of insulin glargine and zinc content. See Table 1 for details.

Table 1. Composition of the U300 cartridge and U100 formulations.

|                               | To-be-marketed insulin glargine solution for injection<br>300 U/mL,<br>1.5 mL cartridge<br>[mg/mL] | Insulin glargine solution for injection<br>300 U/mL,<br>(b) (4) mL cartridge<br>(investigational use only)<br>[mg/mL] | Commercialized insulin glargine (LANTUS) solution for injection 100 U/mL<br>3 mL cartridge<br>[mg/mL] |
|-------------------------------|--|---|---|
| Insulin glargine              |  | 10.91   | 3.64 (b) (4)  |
| Zinc                          |  |   |   |
| Glycerol (85%)                |  |   |   |
| Metacresol                    |  |   |   |
| Sodium hydroxide              |  |   |   |
| Hydrochloric acid,<br>(b) (4) |  |   |   |
| Water for injection           |  |   |   |

Source: Sponsor’s Section 2.3.P.2 Table 2.

#### 2.1.2 Is there any difference between the clinically-tested formulation of U300 and the to-be-marketed formulation of U300?

No difference exists between the clinically tested U300 cartridge formulation (investigational use) and the to-be-marketed U300 cartridge formulation as shown in Table 1. (b) (4)

(b) (4) See Table 2 for the composition of the cartridge (b) (4) formulations. The sponsor conducted Study PKD13560 to address the bioequivalence between the (b) (4) cartridge formulation and the (b) (4) formulation of U300.

Table 2. Composition of the U300 cartridge (b) (4) formulations.

| Ingredient        | Function       | Strength (300 U/mL)  |                |
|-------------------|----------------|----------------------|----------------|
|                   |                | (b) (4) mL cartridge |                |
|                   |                | mg/mL                | % <sup>a</sup> |
| Insulin glargine  | Drug substance | 10.91                | 1.1            |
| Glycerol 85%      |                |                      |                |
| Metacresol        |                |                      |                |
| Zinc              |                |                      |                |
| Hydrochloric acid |                |                      |                |
| Sodium            |                |                      |                |
| Water for         |                |                      |                |

<sup>a</sup> each ingredient expressed as a percentage w/v % for solutions

Source: Sponsor's Section 2.7.1 Table 7.

## 2.2 Key Clinical Pharmacology Questions

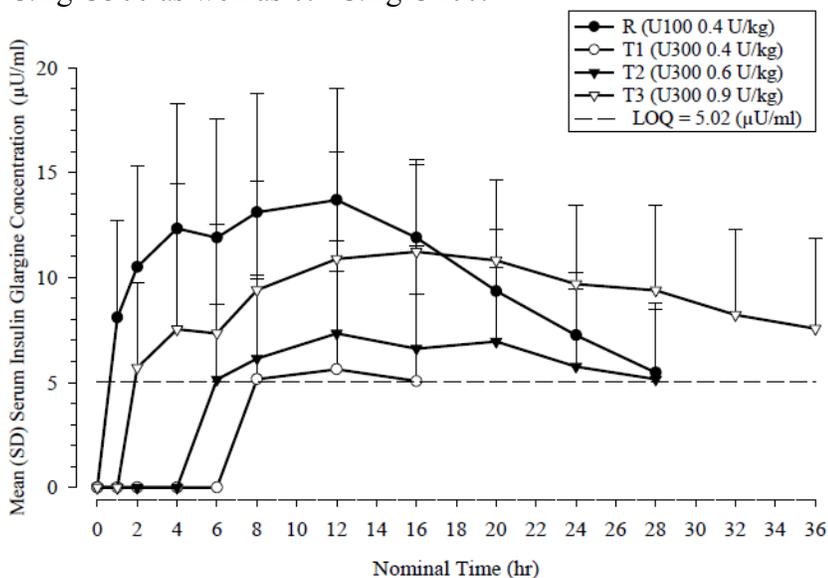
### 2.2.1 What are the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of U300 upon SC administration?

#### Single Dose

Study PKD11627 assessed the PK and PD of SC single rising doses of 0.4, 0.6, and 0.9 U/kg U300 as well as 0.4 U/kg U100 (Lantus) in a 4-sequence crossover design with 5 – 18 days as washouts in 24 T1DM patients. The SC injection site was the periumbilical area. Serial serum samples were collected predose and 36 hours postdose to determine the insulin glargine concentration via a validated radioimmunoassay (RIA). After the respective dosing, blood glucose (BG) concentrations of the patients were maintained within a range of 5.6 mmol/L (100 mg/dL) ± 20% via the intravenous infusion of glucose solution (euglycemic clamp) until 36 hours postdose (clamp end). The glucose infusion rate (GIR) is a measure of the PD response.

Figure 1 shows the mean (SD) serum insulin glargine concentration versus time profiles of 0.4, 0.6, and 0.9 U/kg U300 as well as 0.4 U/kg U100. The concentration-time profile for insulin glargine U300 treatments (T1 to T3) were relatively flat 8 – 16 hours, 8 – 28 hours, and 8 – 36 hours for the 0.4 U/kg, 0.6 U/kg, and 0.9 U/kg U300, respectively. Upon SC injection of 0.4 U/kg U100 (R), serum insulin glargine concentrations increased to 12 hours and then decline to 28 hours within quantitation limit. In general, the mean serum insulin glargine concentration versus time profiles of 0.4, 0.6, and 0.9 U/kg U300 are flatter than that of the 0.4 U/kg U100.

Figure 1. Mean (SD) serum insulin glargine concentration-time profiles of single dose 0.4, 0.6, and 0.9 U/kg U300 as well as 0.4 U/kg U100.



Source: Study PKD11627 Report, Figure 8, Page 106/126

Table 3. Mean ± SD PK parameters of single doses 0.4 U/kg U100 as well as 0.4, 0.6, and 0.9 U/kg U300

| Mean ± SD<br>(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 <sup>b</sup>                            | 22                           | 15 <sup>c</sup>              | 20 <sup>d</sup>              | 22                           |
| INS-C <sub>max</sub><br>(µU/ml)           | 15.3 ± 5.95<br>(14.2) [38.9] | 8.94 ± 2.89<br>(8.57) [32.3] | 9.26 ± 2.79<br>(8.87) [30.2] | 13.0 ± 6.16<br>(11.8) [47.2] |
| INS-T <sub>max</sub> <sup>a</sup><br>(hr) | 12.00<br>(2.00 - 16.00)      | 12.00<br>(1.00 - 36.00)      | 12.00<br>(1.00 - 36.00)      | 16.00<br>(4.00 - 36.00)      |
| INS-AUC <sub>0-36</sub><br>(µU•hr/ml)     | 318 ± 109<br>(280) [34.3]    | 195 ± 89.1<br>(177) [45.6]   | 206 ± 105<br>(166) [51.0]    | 327 ± 139<br>(288) [42.6]    |
| INS-AUC <sub>0-24</sub><br>(µU•hr/ml)     | 266 ± 92.3<br>(236) [34.7]   | 148 ± 63.5<br>(136) [42.9]   | 149 ± 76.1<br>(119) [51.0]   | 222 ± 98.5<br>(196) [44.4]   |

Source: Study PKD11627 Report, Table 22, 108/126

The mean INS-AUC<sub>0-36</sub> for U300 treatments increased with treatments: 195, 206, and 327 µU/mL for T1, T2, and T3, respectively, as compared to 318 µU/mL for treatment R (Table 3). Compared to R, the exposure over the clamp period of 36 hours (INS-AUC<sub>0-36</sub>) was significantly lower for T1 and T2 and similar for T3. For U300, the INS-C<sub>max</sub> of T1 and T2 were about 9 µU/mL, while INS-C<sub>max</sub> of T3 was 13.0 µU/mL. Treatment R showed the highest INS-C<sub>max</sub> of 15.3 µU/mL (Table 3).

Figure 2a. Mean smoothed body weight standardized GIR profiles over time for Study PKD 11627

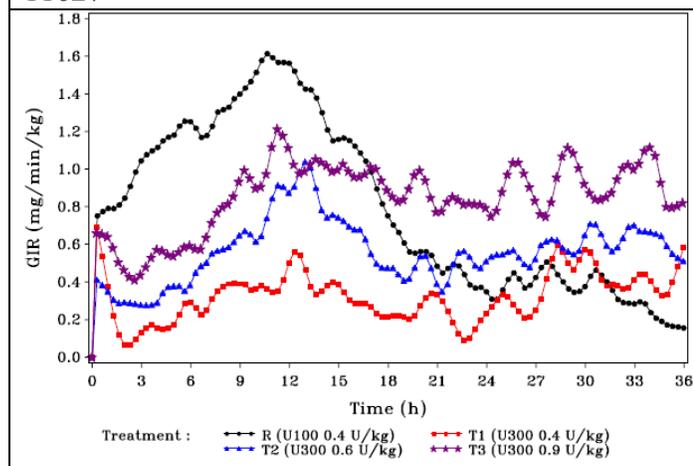
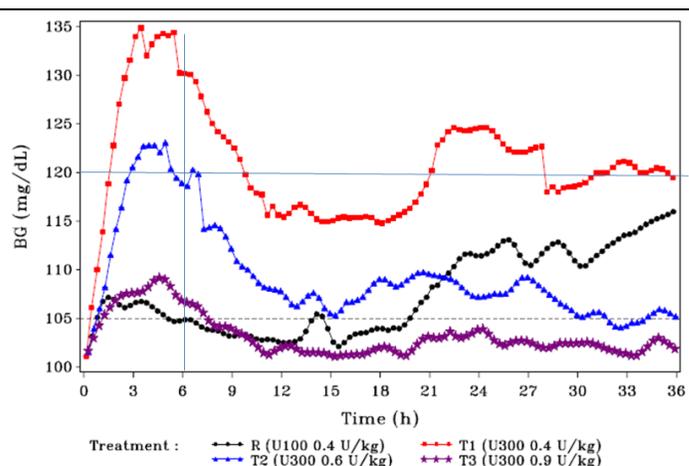


Figure 2b. Mean smoothed blood glucose profiles over time for Study PKD 11627



Source: Study PKD11627's Report, Figure 3, Page 85/126 and Figure 7, Page 94/126, respectively

GIR profiles for U300 treatments T1 to T3 showed a trend for the dose-dependent increase over the 36 hours clamp observation period after dosing (Figure 2a). GIR for T1 to T3 increased from 3 hours onwards to a maximum at around 12 hours. Thereafter, GIR for T1 to T3 slightly declined, but eventually remained fairly stable up to the end of the clamp. GIR over the first 6 hours of single dose administrations is associated with blood glucose concentrations that exceed the prespecified clamp target of 5.6 mmol/L (100 mg/dL)  $\pm$  20% (Figure 2b). Thus, Figures 2a and 2b show that U300's time to onset of action after the 1<sup>st</sup> dose on average was about 6 hours.

Table 4. Descriptive statistics of area under the body weight standardized glucose infusion rate time curve upon SC single dose administration.

|  | R (U100 0.4 U/kg) | T1 (U300 0.4 U/kg) | Test treatment     |                    |
|--|-------------------|--------------------|--------------------|--------------------|
|  |                   |                    | T2 (U300 0.6 U/kg) | T3 (U300 0.9 U/kg) |
| <b>GIR-AUC<sub>0-24h</sub> (mg/kg)</b> |                   |                    |                    |                    |
| Number                                 | 22                | 22                 | 22                 | 22                 |
| Geometric Mean                         | 1086.84           | 96.36              | 271.73             | 992.56             |
| CV%                                    | 54.748            | 98.976             | 107.012            | 51.568             |
| Mean (SD)                              | 1479.84 (810.19)  | 382.97 (379.05)    | 727.68 (778.70)    | 1178.65 (607.80)   |
| Median                                 | 1361.15           | 226.65             | 481.35             | 1098.65            |
| Min : Max                              | 5.3 : 3734.9      | 1.0 : 1154.6       | 1.0 : 3072.7       | 124.7 : 2375.8     |
| <b>GIR-AUC<sub>0-36h</sub> (mg/kg)</b> |                   |                    |                    |                    |
| 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     |

Source: Modified from Study PKD11627's Report, Table 9, 86/126

The GIR-AUC<sub>0-24h</sub> and GIR-AUC<sub>0-36h</sub> all show the trend of dose-dependent increase (Table 4).

Table 5. GIR (body weight standardized) - estimates of treatment ratio with 90% CI upon single SC administration

| Parameter                        | Treatment Ratio               | Estimate | 90% CI      |
|----------------------------------|-------------------------------|----------|-------------|
| GIR-AUC <sub>0-36h</sub> [mg/kg] | 0.4 U/kg U300 ÷ 0.4 U/kg U100 | 0.12     | 0.05 – 0.30 |
|                                  | 0.6 U/kg U300 ÷ 0.4 U/kg U100 | 0.33     | 0.17 – 0.66 |
|                                  | 0.9 U/kg U300 ÷ 0.4 U/kg U100 | 1.37     | 0.89 – 2.13 |
| GIR-AUC <sub>0-24h</sub> [mg/kg] | 0.4 U/kg U300 ÷ 0.4 U/kg U100 | 0.09     | 0.04 – 0.21 |
|                                  | 0.6 U/kg U300 ÷ 0.4 U/kg U100 | 0.25     | 0.13 – 0.49 |
|                                  | 0.9 U/kg U300 ÷ 0.4 U/kg U100 | 0.93     | 0.59 – 1.48 |
| GIR <sub>max</sub> [mg/kg/min]   | 0.4 U/kg U300 ÷ 0.4 U/kg U100 | 0.23     | 0.08 – 0.63 |
|                                  | 0.6 U/kg U300 ÷ 0.4 U/kg U100 | 0.49     | 0.26 – 0.89 |
|                                  | 0.9 U/kg U300 ÷ 0.4 U/kg U100 | 1.11     | 0.83 – 1.48 |

Source: Modified from Study PKD11627's Report, Table 10, 87/126

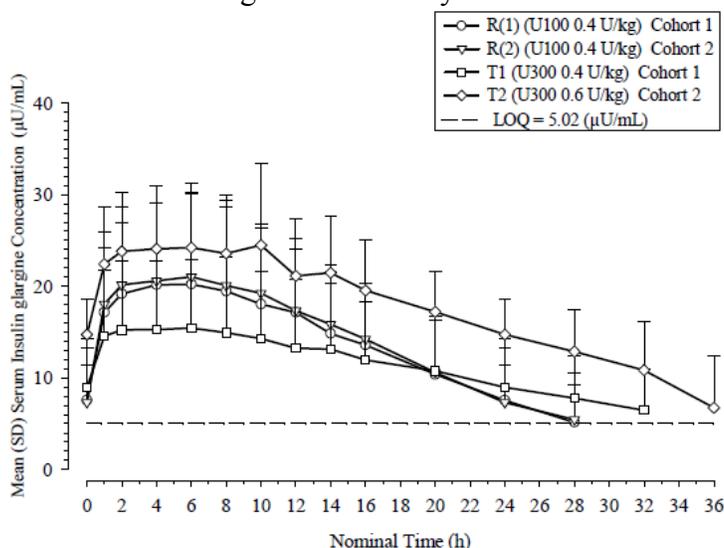
Treatments T1 and T2 required an overall lower amount of exogenously administered glucose (GIR-AUC<sub>0-36</sub>) compared to R but T3 GIR-AUC<sub>0-36</sub> was greater than that of R (Table 5).

### Multiple Doses

Study TDR11626 compared the PK and PD of 8 daily SC doses of 0.4 U/kg U300 (T1) with 0.4 U/kg of LANTUS (R1) in a cohort of 18 T1DM patients and the PK and PD of 8 daily SC doses of 0.6 U/kg U300 (T2) with 0.4 U/kg of LANTUS (R2) in another cohort of 12 T1DM patients. The SC injection site was the periumbilical area. Serial serum samples were collected on Day 8 predose and for 36 hours postdose to determine the insulin glargine concentration via a validated RIA. The RIA is not specific to insulin glargine as well as to its M1 and M2 metabolites. Thus, the sponsor also collected plasma samples at predose daily for 8 days and collected serial plasma samples for 36 hours postdose on Day 8 to measure insulin glargine and its M1 and M2 metabolites concentrations via a validated LC-MS/MS.

After the 8<sup>th</sup> daily dosing, BG concentrations of the patients were maintained within a range of 5.6 mmol/L (100 mg/dL) ± 20% via intravenous infusion of glucose solution (euglycemic clamp) until 36 hours postdose (clamp end). The GIR is a measure of the PD response.

Figure 3. Mean (SD) serum insulin glargine concentration-time profiles of 0.4 and 0.6 U/kg U300 as well as 0.4 and 0.4 U/kg U100 at steady state.



The steady state profiles of serum insulin glargine for treatments with U300, 0.4 U/kg (T1) and 0.6 U/kg (T2), were generally flat and displayed detectable exposure and the corresponding mean concentrations until 32 and 36 hours postdose, respectively (Figure 3). The mean insulin glargine concentrations for the reference treatments with 0.4 U/kg U100 R1 and R2 were nearly overlapping. Serum insulin glargine concentrations were quantifiable until 28 hours after SC administration of U100.

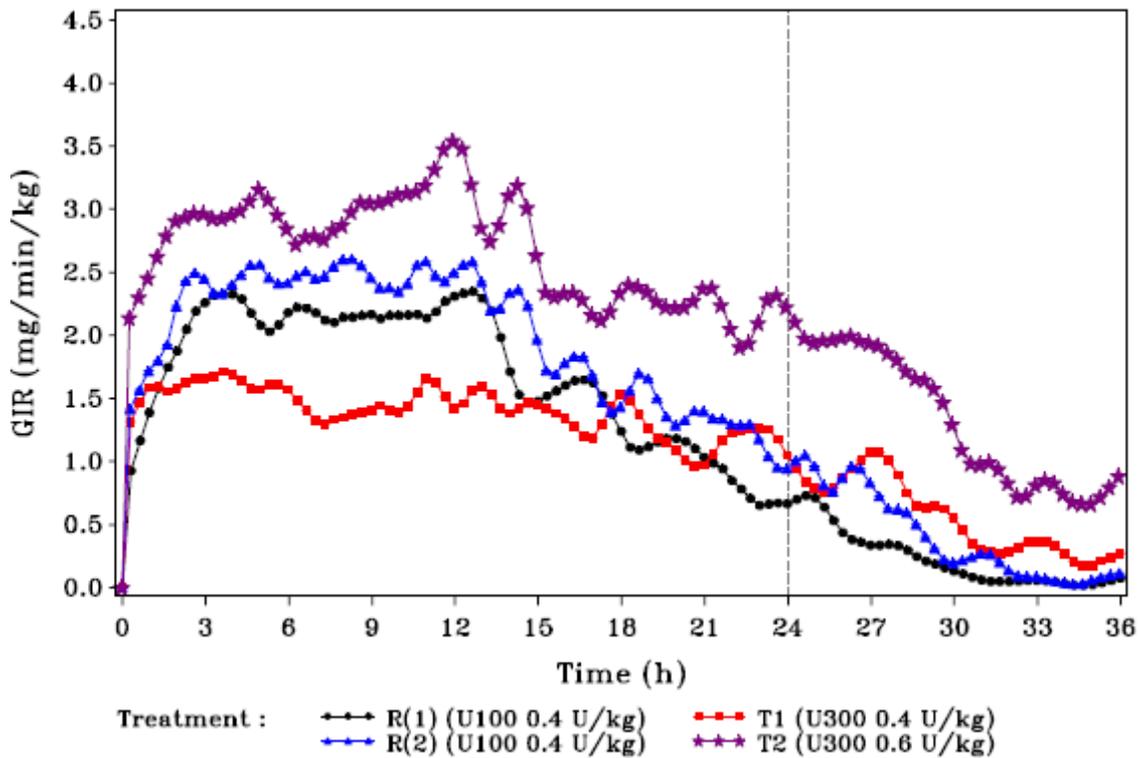
Table 6. Mean  $\pm$  SD PK parameters of U100 0.4 U/kg, U300 0.4 U/kg, U100 0.4 kg, and U300 0.6 U/kg

|  | R(1)<br>(U100 0.4 U/kg)          | T1<br>(U300 0.4 U/kg)                         | R(2)<br>(U100 0.4 U/kg)                       | T2<br>(U300 0.6 U/kg)            |
|--|----------------------------------|---|---|----------------------------------|
|  | Cohort 1                         |   | Cohort 2                                      |                                  |
| N  | 17*                              | 16**  | 12  | 12                               |
| INS-C <sub>max</sub><br>( $\mu$ U/mL)      | 23.4 $\pm$ 8.36<br>(21.7) [35.7] | 18.1 $\pm$ 6.51<br>(16.8) [35.9]              | 22.8 $\pm$ 8.03<br>(20.8) [35.2]              | 27.2 $\pm$ 8.58<br>(25.4) [31.6] |
| INS-T <sub>max</sub> <sup>a</sup><br>(h)   | 4<br>(2.00 - 12.00)              | 5<br>(1.00 - 14.00)                           | 6<br>(2.00 - 10.00)                           | 6<br>(1.00 - 10.00)              |
| INS-t <sub>1/2z</sub><br>(h)               | 13.5 $\pm$ 6.91<br>(12.1) [51.1] | 19.0 $\pm$ 6.35<br>(18.1) [33.4] <sup>b</sup> | 10.8 $\pm$ 4.27<br>(9.88) [39.6] <sup>c</sup> | 17.7 $\pm$ 11.4<br>(14.9) [64.7] |
| INS-AUC <sub>0-36</sub><br>( $\mu$ U·h/mL) | 438 $\pm$ 167<br>(396) [38.1]    | 418 $\pm$ 186<br>(360) [44.5]                 | 436 $\pm$ 199<br>(367) [45.7]                 | 638 $\pm$ 167<br>(607) [26.2]    |
| INS-AUC <sub>0-24</sub><br>( $\mu$ U·h/mL) | 389 $\pm$ 141<br>(356) [36.2]    | 331 $\pm$ 140<br>(291) [42.4]                 | 380 $\pm$ 157<br>(329) [41.3]                 | 500 $\pm$ 131<br>(477) [26.2]    |

Source: Study TDR11626 Report, Table 35, 128/162

U300 showed longer mean terminal half-life, INS-t<sub>1/2z</sub>, 19.0 hours for T1 and 17.7 hours for T2, than those for R1 and R2 (13.5 hours for R1 and 10.8 hours for R2) (Table 6). The mean total exposure at steady-state (INS-AUC<sub>0-24</sub>) for R1 and R2 of 0.4 U/kg U100 were similar (389  $\mu$ U·h/mL and 380  $\mu$ U·h/mL). Among the 0.4 U/kg U300 (T1) and 0.6 U/kg U300 (T2) doses, the mean daily total exposure was 331  $\mu$ U·h/mL and 500  $\mu$ U·h/mL, respectively, that showed an approximate increase in proportion to the dose. The mean total exposures of insulin glargine over the entire clamp period (INS-AUC<sub>0-36</sub>) showed similar trend.

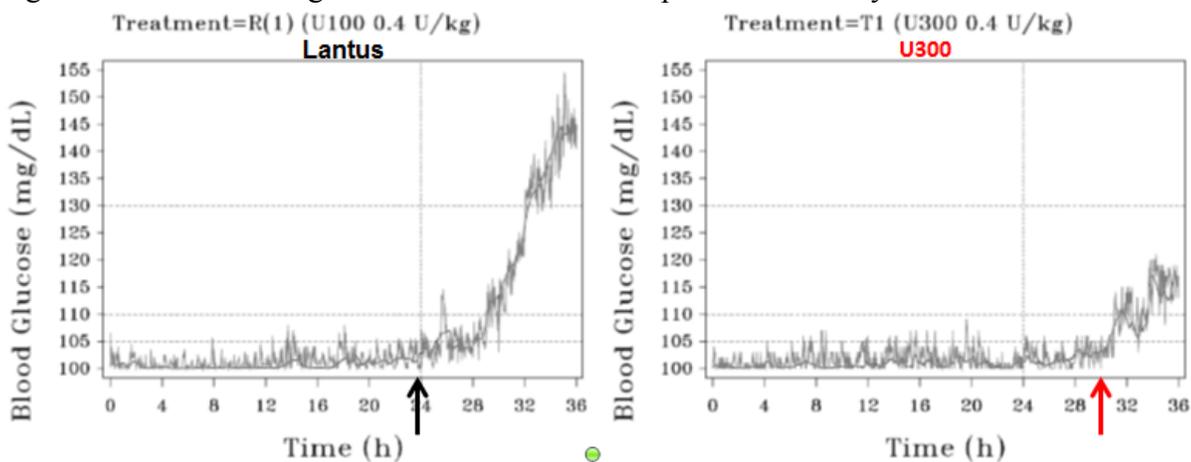
Figure 4. Mean smoothed body weight-standardized GIR profiles over time for Study TDR11626.



Source: Study TDR11626 Report, Figure 4, 92/162

The mean smoothed body weight-standardized GIR curve of 0.4 U/kg U300 (T1) forms a plateau below the curves of 0.4 U/kg U100 (R1 and R2) for about 15 hours postdose (Figure 4). Thereafter, the curves of R1 and R2 cross over the curve of T1 indicating an earlier end of the comparator action. Figure 5 shows that the effect of 0.4 U/kg U300 to maintain the median blood glucose concentrations persists beyond 24 hours upon once daily dosing at steady state in euglycemic clamp. The mean smoothed body weight-standardized GIR curve of 0.6 U/kg U300 (T2) was higher than those of 0.4 U/kg U100 (R1 and R2) at all time points, with a decline beyond 24 hours up to the end of clamp (at 36 hours).

Figure 5. Median blood glucose concentration-time profiles for Study TDR11626



Source: Modified from Study TDR11626 Report, Figure 7 Page 100/162

Table 7. GIR point estimates of ratios between U300 and U100 and their 90% CI and 95% CI upon multiple SC administration

| Treatment Ratio | Parameter | Estimate | 90% CI | 95% CI |
|-----------------|-----------|----------|--------|--------|
|-----------------|-----------|----------|--------|--------|

|                               |                          |      |             |             |
|-------------------------------|--------------------------|------|-------------|-------------|
| 0.4 U/kg U300 ÷ 0.4 U/kg U100 | GIR <sub>max</sub>       | 0.81 | 0.68 – 0.97 | 0.65 – 1.01 |
|                               | GIR-AUC <sub>0-24h</sub> | 0.73 | 0.56 – 0.94 | 0.53 – 0.99 |
|                               | GIR-AUC <sub>0-36h</sub> | 0.85 | 0.70 – 1.03 | 0.67 – 1.08 |
| 0.6 U/kg U300 ÷ 0.4 U/kg U100 | GIR <sub>max</sub>       | 1.20 | 0.88 – 1.62 | 0.83 – 1.73 |
|                               | GIR-AUC <sub>0-24h</sub> | 1.46 | 0.96 – 2.21 | 0.88 – 2.43 |
|                               | GIR-AUC <sub>0-36h</sub> | 1.65 | 1.11 – 2.46 | 1.02 – 2.70 |

Source: Modified from Study TDR11626 Report, Tables 12 and 13, Pages 94 and 95/162

Patients required less glucose (as measured by GIR-AUC) on 0.4 U/kg U300 (T1) than on 0.4 U/kg U100 (R1) to maintain BG control within the first 24 hours of the clamp period showing that the PD response from U300 is lower than U100 on a unit-to-unit basis at steady-state. (Table 7). For 0.4 U/kg U300 (T1), 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 U300 (T2) required more glucose than on 0.4 U/kg U100 (R2) to maintain BG control during clamp within 24 hours and beyond. For 0.6 U/kg U300 (T2), the ratios of geometric means of its GIR-AUC over those of 0.4 U/kg U100 (R2) 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.

### 2.2.2 Is the U300 PK dose proportional upon SC administration?

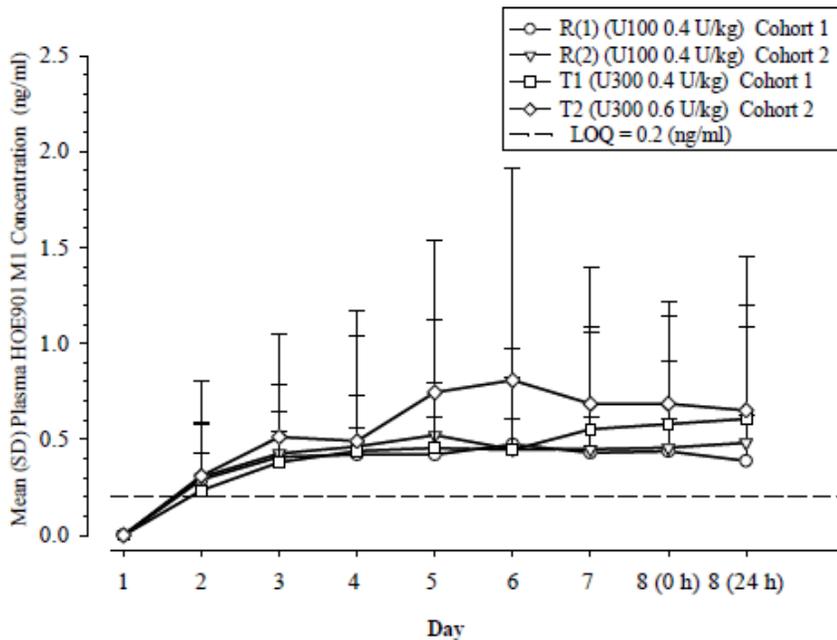
See Question 2.2.1 for the details of Study PKD11627. Per the power model to assess dose-proportionality ( $C_{max}$  or  $AUC_{0-time} = \alpha \cdot [Dose]^{\beta}$ ;  $\alpha$  depends on the subject and error;  $\beta$  is the dose-proportionality factor; after transformation,  $\ln C_{max}$  or  $\ln AUC_{0-time} = \ln \alpha + \beta \cdot \ln SC \text{ Dose}$ ;  $\beta = 1$  when dose-proportional) (Gough et al. *Drug Info J* 1995;29:1039-48). This reviewer performed the subsequent power model analyses.

The slope,  $\beta$ , and its (90% CI) for the  $\ln C_{max}$  vs.  $\ln SC \text{ U300 Dose}$  plot was 0.420 (0.169 – 0.671). The slope,  $\beta$ , and its (90% CI) for the  $\ln AUC_{0-24}$  vs.  $\ln SC \text{ U300 Dose}$  plot,  $\ln AUC_{0-30}$  vs.  $\ln SC \text{ U300 Dose}$  plot, and  $\ln AUC_{0-36}$  vs.  $\ln SC \text{ U300 Dose}$  plot were 0.510 (0.053 – 0.967), 0.595 (0.139 – 1.051), and 0.649 (0.176 – 1.121), respectively. The slope,  $\beta$ , of the power model analyses are all < 1. Thus, the PK of U300 is less than dose proportional for single SC doses from 0.4 U/kg to 0.9 U/kg in T1DM patients.

### 2.2.3 When does U300 reach steady state upon multiple SC administration?

See Question 2.2.1 for the details of Study TDR11626. The daily predose plasma insulin glargine concentrations were quantifiable in 1 of 12 patients in both the 0.4 U/kg U300 dose group and the 0.6 U/kg U300 dose group (Study TDR11626's report 16.2.5 Compliance and drug concentration data Pages 372 and 375/1906). Thus, it is difficult to determine the time for U300 to reach steady state thru assessment of predose plasma insulin glargine concentrations. Visual inspection showed that insulin glargine's M1 metabolite (major circulating metabolite) reached steady state on Day 7 in the 0.4 U/kg daily dose group and on Day 5 in the 0.6 U/kg daily dose group (Figure 6). However, insulin glargine and M2 PK parameters are quantifiable only in some patients.

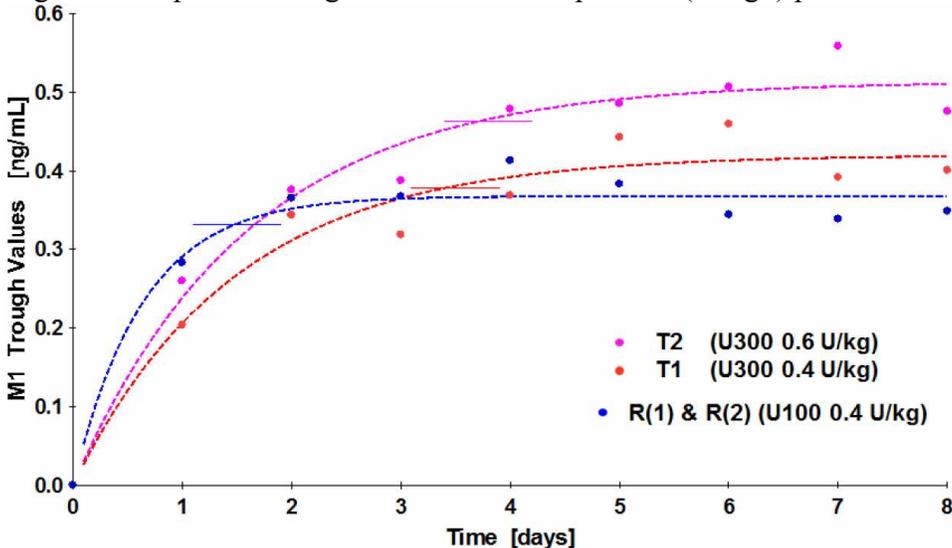
Figure 6. Mean (SD) predose insulin glargine M1 concentration-time profile.



Source: Study TDR11626's report Figure 23, Page 156/162.

The sponsor defined steady state as the achievement of  $\geq 90\%$  of stable plateau. The sponsor plotted the median predose M1 concentration over time (t) by treatment and performed an exponential regression of the data  $\{C_{\text{predose}}=a(1-\exp(-b*t))\}$  (Section 2.7.2 Summary of Clinical Pharmacology Studies Pages 51 and 52/78). The resulting parameters are  $a=0.3681$ ,  $b=1.5667$  (R1 and R2);  $a=0.4206$ ,  $b=0.6749$  (T1); and  $a=0.5141$ ,  $b=0.6234$  (T2). Figure 6 shows these median predose plasma M1 concentrations with the result of the regression, and additional horizontal lines to indicate when 90% of the plateau is reached. For U100, this value is reached at 1.5 days whereas for U300 it is reached at 3.4 to 3.7 days.

Figure 7. Exponential regression of median predose (trough) plasma M1 concentration versus time plots.



Source: Section 2.7.2, Summary of Clinical Pharmacology Studies Figure 19, Page 52/78.

The sponsor reported different times to reach steady state for the daily U300 SC injection in T1DM patients as the following:

- 5 – 7 days; on Day 5 under 0.6 U/kg dosing and on Day 7 under 0.4 U/kg dosing (Study TDR11626's report Section 13.4.2.3 Page 156/1906)

- the 2<sup>nd</sup> to 3<sup>rd</sup> daily U300 injection (2.7.3 Summary of Efficacy Section 4, Page 127/163 and Study PKD12270’s report, Page 29/125)
- 3.4 to 3.7 days thru the exponential regression as described above and proposed that “Steady state level is reached after 3 – 4 days of daily TOUJEO administration.” in Section 12.3 of TOUJEO’s label. The sponsor did not justify the validity of this exponential regression “ $\{C_{predose}=a(1-\exp(-b*t))\}$ ” to describe the relationship between median predose plasma M1 concentration and time postdose.

Consistent with the 21 – 24 hours terminal half-life of plasma M1, this reviewer recommends that U300 reaches steady state in 5 – 7 days after daily 0.4 U/kg to 0.6 U/kg SC administration in T1DM patients.

#### 2.2.4 What is the intra-subject variability of U300 PK and PD parameters?

The sponsor used Study PKD13560 to assess the intra-subject variability of U300 exposure. Study PKD13560 compared 2 different U300 formulations. Thus, Study PKD13560 may be inappropriate for intra-subject variability assessment. However, data from replicate-design study is the proper approach to assess intra-subject variability.

This reviewer chose Study PKD10086 to assess the intra-subject variability because of the replicate design. Study PKD10086 assessed the PK and PD of 2 replicate single SC doses of 0.4 U/kg U300 and 2 replicate single SC doses of 0.4 U/kg U100 via euglycemic clamp in healthy volunteers. The SC injection site was the periumbilical area. The sponsor collected serial serum samples predose and up to 30 hours postdose to measure insulin glargine and C-peptide concentrations via validated bioanalytical assays. Table 8 shows the intra-subject variability of PK and PD for U300 and U100 as coefficient of variation (CV). For U300, the intra-subject variability for INS-AUC<sub>0-24</sub> and INS-C<sub>max</sub> are 21% and 25.6%, respectively, whereas the intra-subject variability for GIR-AUC<sub>0-24</sub> and GIR<sub>max</sub> are 40.3% and 41.3%, respectively. The intra-subject variability of U300 is higher than those of U100 for insulin glargine PK and PD parameters.

Table 8. Intra-subject variability of U300 and U100 for Study PKD10086.

| Parameter               | U300’s Intra-subject Variability, CV% | U100’s Intra-subject Variability, CV% |
|-------------------------|---------------------------------------|---------------------------------------|
| INS-AUC <sub>0-24</sub> | 21.0                                  | 16.2                                  |
| INS-C <sub>max</sub>    | 25.6                                  | 20.0                                  |
| GIR-AUC <sub>0-24</sub> | 40.3                                  | 19.6                                  |
| GIR <sub>max</sub>      | 41.3                                  | 24.5                                  |

Source: Reviewer’s analysis.

#### 2.2.5

(b) (4)



Table 5 (repeated). GIR (body weight standardized) - estimates of treatment ratio with 90% CI upon single SC administration

| Parameter                        | Treatment Ratio               | Estimate | 90% CI      |
|----------------------------------|-------------------------------|----------|-------------|
| GIR-AUC <sub>0-36h</sub> [mg/kg] | 0.4 U/kg U300 ÷ 0.4 U/kg U100 | 0.12     | 0.05 – 0.30 |
|                                  | 0.6 U/kg U300 ÷ 0.4 U/kg U100 | 0.33     | 0.17 – 0.66 |
|                                  | 0.9 U/kg U300 ÷ 0.4 U/kg U100 | 1.37     | 0.89 – 2.13 |
| GIR-AUC <sub>0-24h</sub> [mg/kg] | 0.4 U/kg U300 ÷ 0.4 U/kg U100 | 0.09     | 0.04 – 0.21 |
|                                  | 0.6 U/kg U300 ÷ 0.4 U/kg U100 | 0.25     | 0.13 – 0.49 |
|                                  | 0.9 U/kg U300 ÷ 0.4 U/kg U100 | 0.93     | 0.59 – 1.48 |
| GIR <sub>max</sub> [mg/kg/min]   | 0.4 U/kg U300 ÷ 0.4 U/kg U100 | 0.23     | 0.08 – 0.63 |
|                                  | 0.6 U/kg U300 ÷ 0.4 U/kg U100 | 0.49     | 0.26 – 0.89 |
|                                  | 0.9 U/kg U300 ÷ 0.4 U/kg U100 | 1.11     | 0.83 – 1.48 |

Source: Modified from Study PKD11627's Report, Table 10, 87/126

Table 7 (repeated). GIR point estimates of ratios between U300 and U100 and their 90% CI and 95% CI upon multiple SC administration

| Treatment Ratio               | Parameter                | Estimate | 90% CI      | 95% CI      |
|-------------------------------|--------------------------|----------|-------------|-------------|
| 0.4 U/kg U300 ÷ 0.4 U/kg U100 | GIR <sub>max</sub>       | 0.81     | 0.68 – 0.97 | 0.65 – 1.01 |
|                               | GIR-AUC <sub>0-24h</sub> | 0.73     | 0.56 – 0.94 | 0.53 – 0.99 |
|                               | GIR-AUC <sub>0-36h</sub> | 0.85     | 0.70 – 1.03 | 0.67 – 1.08 |
| 0.6 U/kg U300 ÷ 0.4 U/kg U100 | GIR <sub>max</sub>       | 1.20     | 0.88 – 1.62 | 0.83 – 1.73 |
|                               | GIR-AUC <sub>0-24h</sub> | 1.46     | 0.96 – 2.21 | 0.88 – 2.43 |
|                               | GIR-AUC <sub>0-36h</sub> | 1.65     | 1.11 – 2.46 | 1.02 – 2.70 |

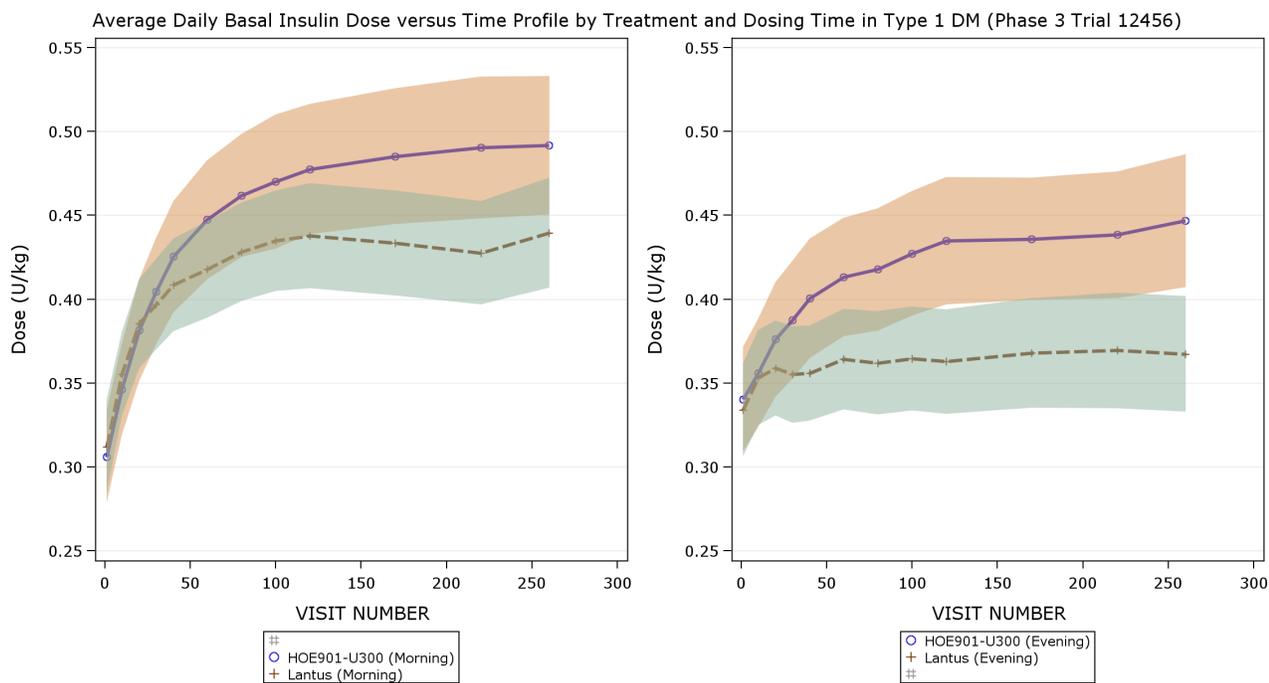
Source: Modified from Study TDR11626 Report, Tables 12 and 13, Pages 94 and 95/162

However, the 4 clinical efficacy and safety trials for T1DM and T2DM patients show that U300 is non-inferior to U100 in terms of lowering hemoglobin A1C (efficacy measurement) with comparable adverse events between U300 and U100 especially for hypoglycemia.

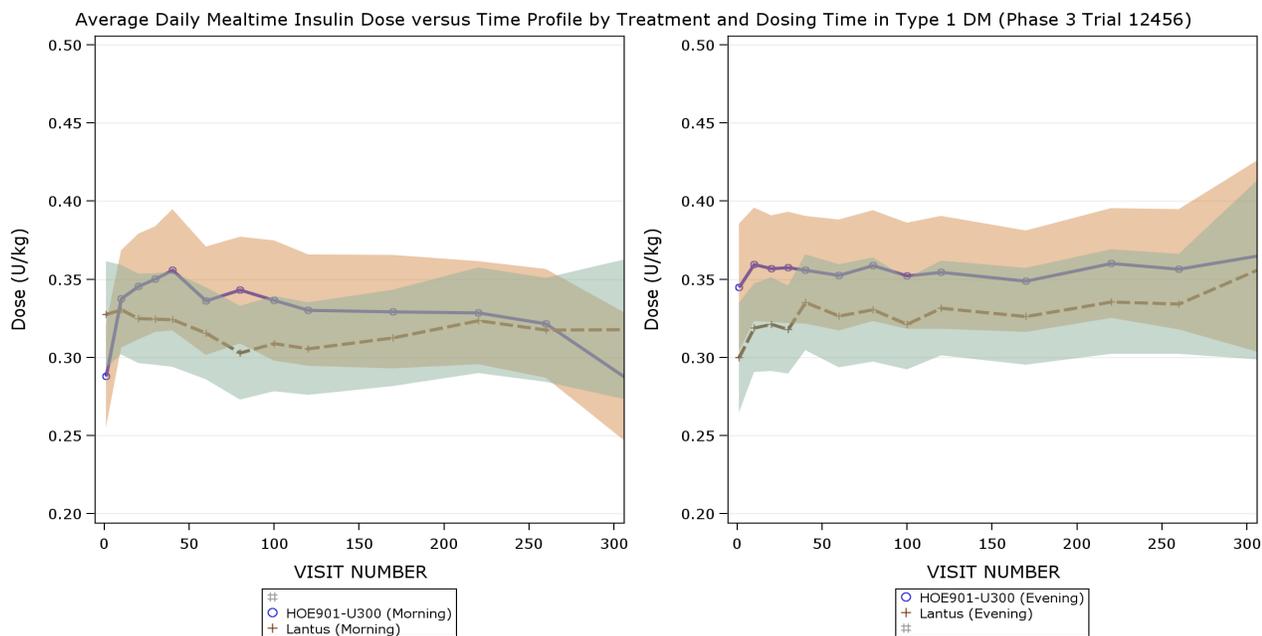
After single subcutaneous administration, U300 demonstrated slower absorption and substantially lower relative bioavailability when compared to Lantus on a unit-to-unit dose basis (0.4 U/kg dose). This translated to significantly lower glucose lowering effect: geometric mean ratio of 12% (90%CI of 5 – 30%) for AUC under glucose infusion rate versus time curve (GIR-AUC<sub>0-36h</sub>). After multiple once daily SC administration, U300 demonstrated slower absorption and lower relative bioavailability when compared to Lantus on a unit-to-unit dose basis (0.4 U/kg dose). At steady-state, the average glucose lowering effect was still lower than Lantus: geometric mean ratio of 73% (90%CI of 56 – 94%) for GIR-AUC<sub>0-24h</sub> (or GIRAUC<sub>0-tau</sub>) versus Lantus. However, due to accumulation of insulin after multiple doses, the magnitude of difference in response between U300 and Lantus was reduced keeping single dose comparison results in perspective.

This difference in the glucose lowering effect on a unit-to-unit dose basis was consistent with the higher average basal insulin unit dose utilization in the Phase 3 efficacy/safety trials in both type 1 diabetes and type 2 diabetes patients (see Figures 8 and 9. The average meal-time insulin dose was more or less similar, albeit slightly higher in U300 arm in the studies conducted with bolus/basal combination (e.g. see Figure 7 for data from Type 1 DM).

Figure 8. Average daily basal insulin dose (upper panel) and meal-time (lower panel) insulin by treatment and dosing time in patients with type 1 diabetes



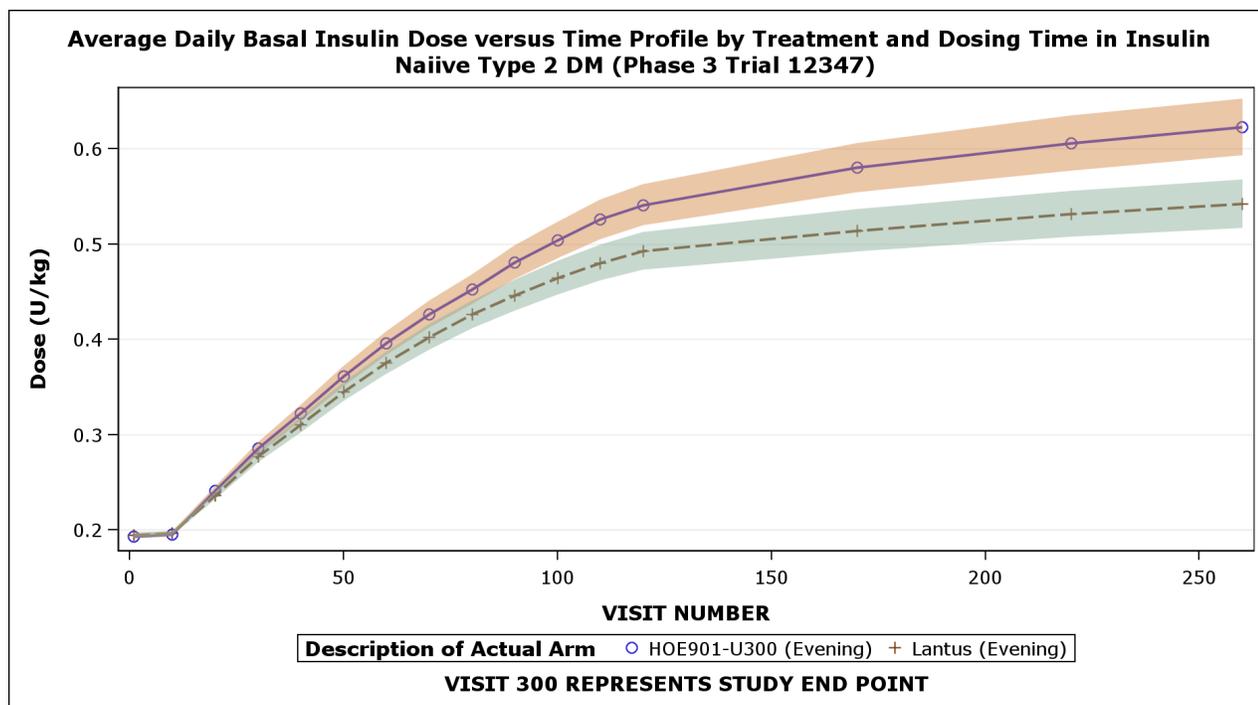
Source: Reviewer's analysis



These data support the administration of U300 in the evening because of lower mean unit dose usage than those observed in the morning administration of U300, while being within the range of mean unit dose for morning or evening administration of U100 in T1DM patients. The meal time insulin usage was similar between morning and evening administration of U100. The evening administration will limit the undue escalation of TOUJEO dose in patients with T1DM.

In the efficacy and safety trials in patients with T2DM, the U300 or U100 were administered in the evening.

Figure 9. Average daily basal insulin dose by treatment and dosing time in insulin naïve patients with type 2 diabetes



Source: Reviewer's analysis

This information needs to be adequately reflected in the label (see labeling recommendations).

Regulatory and clinical implications of PK and PD differences:

- While the potency of the insulin is typically established from in vitro/non-clinical studies, the “Unit Dose” for clinical use is established on the basis of PK/PD data that provides the time-activity profile of an insulin product in addition to the dose-response data. This data is pivotal in making decisions on the time and frequency of administration of the insulin product and choosing the unit dose for clinical evaluation, and later for therapeutic use post-approval. The PK/PD data on unit-to-unit match in glucose lowering response provides a fundamental support for transitioning the patients on unit-to-unit basis from their previous insulin treatments during clinical evaluation, and for labeling recommendations on therapeutic use. Typically, the molar dose ratio assessment is conducted through the dose-response data from PK/PD studies, where the differences in PK/PD profiles (due to in vitro potency or in vivo PK differences) from identical molar dose of test and reference insulin (with established unit dose and formulation strength as Units/mL) is accounted by adjusting the molar strength of the formulation such that “ $X$  nmol/mL” of test insulin constitutes 1 Unit/mL (for example: Insulin detemir is formulated as 2400 nmol/mL yet defined as 100 U/mL<sup>1</sup>). Generation of this data has been more of a necessity rather than a requirement from both regulatory and industry perspective.
- For the reasons mentioned above with TOUJEO, there is an inherent potential of downward drift in the systemic exposure and PD response for a unit dose of insulin (in reference to U100) and the associated molar dose ratio assessment that may be based on TOUJEO in future. If another insulin product uses TOUJEO as a reference for molar dose ratio assessment, this downward drift will

<sup>1</sup> Chemistry Review Levemir NDA 21-536 accessed from [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2005/021-536\\_Levemir\\_chemr.PDF](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021-536_Levemir_chemr.PDF)

eventually cause unnecessary escalation of unit dose requirements in patients without any additional efficacy benefit from the other insulin product. Currently, clinical trials typically assess non-inferiority of hemoglobin A1c as the primary endpoint between an insulin product and its insulin comparator.

- Therefore, TOUJEO may be unsuitable to be considered for molar dose ratio assessment/dose-response comparison in PK/PD studies conducted during the design and development of insulin products.

## 2.2.6

(b) (4)

### 2.2.7 What is the metabolic pathway of U300 and the major circulating metabolite(s) upon U300 SC administration?

Upon subcutaneous injection, insulin glargine undergoes enzymatic removal of the COOH-terminal basic arginine pair from the B-chain and yields the 21A-Gly-human insulin metabolite, M1. Subsequent cleavage of 30-threonine in the B-chain yields the M2 metabolite. See Figure 10 for details.

Figure 10. Metabolic pathway of insulin glargine in humans.

COPYRIGHT MATERIAL

Source: Bolli et al. *Diabetes Care* 2012; 35:2626–30.

In Study TDK11626, the sponsor determined the plasma insulin glargine concentrations as well as plasma insulin glargine's metabolites, M1 and M2, concentrations via a validated LC/MS-MS bioanalytical assay upon daily 0.4 and 0.6 U/kg SC injections to steady state. Across all treatments and the majority of individual samples, the plasma concentration of parent insulin glargine and M2 metabolite were below the lower limit of quantitation of 0.2 ng/mL. The M1 metabolite was the main metabolite in the trough plasma samples and the PK plasma samples after the last dosing on Day 8. M1 has a mean terminal half-life of 21.2 – 24.4 hours in plasma samples, whereas insulin glargine has a terminal half of 17.7 – 19 hours in serum samples at steady state.

## 2.3 Bioanalytical

### 2.3.1 Are the bioanalytical methods properly validated to measure U300?

The sponsor used a radioimmunoassay (RIA) to quantify free insulin glargine in human serum samples (Method VAL030/01). It selectively measures immunoreactive insulin. This assay depends on competition between  $^{125}\text{I}$ -human insulin (tracer) and insulin glargine in standards and test samples (binding to the limited amount of binding sites on guinea pig anti-human insulin antibody). The sponsor used insulin glargine as the reference standard to calibrate the assay. There is a complete cross-reactivity with human insulin and 90% cross-reactivity with the M2 metabolite.

Briefly, the sponsor pretreated 200  $\mu\text{L}$  samples with 25% polyethylene glycol and incubated them (22 – 25°C for 20 – 24 hours) with 100  $\mu\text{L}$  labeled tracer antigen and 100  $\mu\text{L}$  guinea pig anti-human insulin serum. They separated the antibody-bound tracer from the free tracer via precipitation. After decanting the free tracer fraction, they counted the remaining radioactivity for the antibody-bound fraction (B). They then calculated the percentage of maximum binding (% B/B0) for each sample, where B0 represents the maximum (noncompetitive) binding fraction. They used an unweighed 4-parameter logistic regression model to quantify the insulin glargine. The validation results are in Table 9. The sponsor used this assay in Study PKD10086.

Method SPH0296 supplemented Method VAL030/01 via adding an investigation of long-term stability of insulin glargine in human serum stored at -20°C and -70°C up to 2 years. The sponsor evaluated the long-term matrix stability in normal serum from 2 subjects and spiked insulin glargine at 13.5  $\mu\text{U}/\text{mL}$  and 110  $\mu\text{U}/\text{mL}$ . They stored the samples at -20 °C and -70 °C for 1 month, 3 months, 6 months, 1 year, and 2 years and then assayed against a freshly prepared set of calibration standards. The concentrations that were measured for the samples were compared to the T0 (concentration at onset of storage period) concentrations of these samples. The validation results are in Table 9. The sponsor used this assay in Studies PKD11627, TDR11626, PKD12270, PKD13560, and PDY12335.

The sponsor used an LC-MS/MS method to measure insulin glargine and its M1 and M2 metabolites in plasma samples. M1 is the predominant active moiety in human plasma. The LC-MS/MS method was validated following immunoaffinity extraction of [U- $^{15}\text{N}$ ]-HOE901, [U- $^{15}\text{N}$ ]-HOE901-M1 and [U- $^{15}\text{N}$ ]-HOE901-M2 as the internal standards. The validation results are in Table 9. The sponsor used this assay in Study TDR11626.

Insulin glargine was stable in human plasma at 0°C (ice bath) for at least 4 hours, at ambient temperature for at least 4 hours, at approximately -20°C and at approximately -80°C for at least 7 months and following at least 3 freeze/thaw cycles at approximately -20°C and at about -80°C. In addition, processed samples were stable for at least 7 days at room temperature. In blood, HOE901 was stable for 2 hours at 0°C (ice bath). HOE901 was stable in solvent for at least 8 months when stored at approximately -80°C.

M1 was stable in human plasma at 0°C (ice bath) for at least 4 hours, at ambient temperature for at least 4 hours, at about -20°C for 6 months and at about -80°C for at least 7 months and following at least 3 freeze/thaw cycles at about -20°C and at about -80°C. In addition, processed samples were stable for at least 7 days at room temperature. In blood, M1 was stable for at least 4 hours at 0°C (ice bath). M1 was stable in solvent for at least 8 months when stored at about -80°C.

M2 was stable in human plasma at 0°C (ice bath) for at least 4 hours, at ambient temperature for at least 4 hours, at about -20°C for 6 months and at about -80°C for at least 7 months and following at least three freeze/thaw cycles at about -20°C and at about -80°C. In addition, processed samples were stable for at least 7 days at room temperature. In blood, M2 was stable for at least 4 hours at 0°C (ice bath). M2 was stable in solvent for at least 4 months when stored at room temperature.

Table 9. Validation results for the bioanalytical assay of insulin glargine, its metabolites, and C-peptide.

| Study (method)   | Analyte                          | Matrix (anticoag.)               | Calibration range                                     | LLOQ                                | Accuracy <sup>a</sup> (%)              | Within-run precision (%)                        | Between-run precision (%)                       | Clinical studies   |
|--|----------------------------------|----------------------------------|---|-------------------------------------|--|---|---|--|
| VAL030/01<br>(Radioimmuno-precipitation-<br>assay)   | Insulin<br>glargine              | Serum                            | 5.02 to 150 µU/mL                                     | 5.02 µU/mL                          | 0.5 to 8.4%                            | 0.9 to 4.6%                                     | 1.4 to 5.0%                                     | PKD10086   |
| SPH0296  |                                  |                                  |   |                                     |  |   |   | PKD11627<br>TDR11626<br>PKD12270<br>PKD13560<br>PDY12335 |
| DOH1006<br>(LC-MS/MS)  | HOE901<br>HOE901-M1<br>HOE901-M2 | Plasma<br>(K <sub>2</sub> -EDTA) | 0.2 to 10 ng/mL<br>0.2 to 10 ng/mL<br>0.2 to 10 ng/mL | 0.2 ng/mL<br>0.2 ng/mL<br>0.2 ng/mL | 81 to 124%<br>83 to 124%<br>89 to 124% | 4.11 to 8.95%<br>3.35 to 11.1%<br>3.63 to 7.23% | 1.17 to 6.73%<br>2.03 to 6.41%<br>0.72 to 4.26% | TDR11626<br>PKD12270                                     |
| VAL0280/01<br>(Radioimmunoassay)   | C-Peptide                        | Serum                            | 0.300 to 8.00 ng/mL                                   | 0.300 ng/mL                         | -4.4 to 11.0%                          | 1.6 to 6.4%                                     | 1.8 to 3.2%                                     | PKD10086   |
| CI=confidence interval; LC-MS/MS=liquid chromatography tandem mass spectrometry; LLOQ=lower limit of quantitation. <sup>a</sup> The formula for calculation of assay accuracy differs between VAL030/01, VAL028/01, and DOH1006. Therefore, the values fluctuate in the VAL030/01 and VAL028/01 assays around 0 and in the DOH1006 |                                  |                                  |   |                                     |  |   |   |  |

Source: Modified from the sponsor's Section 2.7.1 Table 5. HOE901 is insulin glargine. HOE901-M1 is insulin glargine's M1 metabolite. HOE901-M2 is insulin glargine's M2 metabolite.

The bioanalytical assays for measuring insulin glargine, its M1 and M2 metabolites, and C-peptide are acceptable with reasonable accuracy and precision.

### 3 Preliminary Labeling Recommendations

Strikethrough text means deletion of the sponsor's proposed text. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the sponsor.* See also the approved LANTUS label for reference.

(b) (4)

7 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)  
immediately following this page

4 Appendix  
 4.1 Individual Study Synopses  
 Single Dose PKPD:

**SYNOPSIS**

|   |  |
|---|--|
| <p><b>Title of the study:</b> 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<br/> <b>Study number:</b> PKD11627</p>  |  |
| <p><b>Investigator:</b> Dr. Tim Heise, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, 41460 Neuss, Germany</p>  |  |
| <p><b>Study center:</b> 1 center in Germany</p>   |  |
| <p><b>Publications (reference):</b> Not applicable</p>  |  |
| <p><b>Study period:</b></p> <p style="padding-left: 40px;">Date first patient enrolled: 23 August 2010</p> <p style="padding-left: 40px;">Date last patient completed: 09 December 2010</p>   |  |
| <p><b>Phase of development:</b> Exploratory (Phase 1)</p>   |  |
| <p><b>Objectives:</b></p> <p><u>Primary</u><br/>         To assess the metabolic effect ratios of three different insulin glargine U300 doses versus 0.4 U/kg Lantus® U100.</p> <p><u>Secondary</u><br/>         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 assess the safety and tolerability of insulin glargine U300 in subjects with type 1 diabetes.</p> |  |
| <p><b>Methodology:</b> 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</p>   |  |
| <p><b>Number of patients:</b></p> <p style="padding-left: 40px;">Planned: 24</p> <p style="padding-left: 40px;">Randomized: 24</p> <p style="padding-left: 40px;">Treated: 24</p>   |  |
| <p><b>Evaluated:</b></p> <p style="padding-left: 40px;">Pharmacodynamics: 22</p> <p style="padding-left: 40px;">Safety: 24</p> <p style="padding-left: 40px;">Pharmacokinetics: 22</p>  |  |
| <p><b>Diagnosis and criteria for inclusion:</b> Male and female patients with T1DM, aged 18 to 65 years old</p>   |  |
| <p><b>Investigational product (T [Test]):</b> Insulin glargine 300 U/mL solution for injection (insulin glargine U300)</p> <p style="padding-left: 40px;">Dose: Single dose injection of 0.4 (T<sub>1</sub>), 0.6 (T<sub>2</sub>), and 0.9 U/kg (T<sub>3</sub>) insulin glargine U300</p> <p style="padding-left: 40px;">Administration: Subcutaneous (SC) administration at a periumbilical site of the abdomen, under fasting conditions</p> <p style="padding-left: 40px;">Batch number: C1008260</p>  |  |

**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)

**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

Batch number: 40C280

**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  $GIR-AUC_{0-36}$  ( $T_{50\%}-GIR-AUC_{0-36}$  [hours]);
- Maximum smoothed body-weight-standardized glucose infusion rate ( $GIR_{max}$  [mg\*min/kg]);
- First time after dosing to reach  $GIR_{max}$  ( $GIR-T_{max}$  [hours]);
- Duration of euglycemia (time to elevation of smoothed blood glucose profile above clamp level of 5.6 mmol/L (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 5.8 mmol/L (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 6.1, 7.2, and 8.3 mmol/L (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  $INS-AUC_{0-36}$  ( $T_{50\%}-INS-AUC_{0-36}$ ), maximum concentration observed ( $INS-C_{max}$ ), and first time to reach  $INS-C_{max}$  ( $INS-T_{max}$ ).

**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  $\mu$ U/mL.

**Statistical methods:** Statistical analyses compared reference treatment (R) and test treatments (T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>).

**Pharmacodynamics:** Pharmacodynamic (PD) parameters were summarized by treatment using descriptive statistics. For GIR-AUC<sub>0-36</sub>, the ratios of test (T<sub>1</sub> to T<sub>3</sub>) 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<sub>0-36</sub>. Time to 50% of GIR-AUC<sub>0-36</sub> were compared non-parametrically between T (T<sub>1</sub> to T<sub>3</sub>) and R. GIR-AUC<sub>0-36</sub>, GIR<sub>max</sub>, and GIR-T<sub>max</sub> 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<sub>0-36</sub>, the exposure of T (T<sub>1</sub> to T<sub>3</sub>) 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<sub>0-36</sub>. Time to 50% of INS-AUC<sub>0-36</sub> (T<sub>50%-INS-AUC<sub>0-36</sub></sub>) 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:**

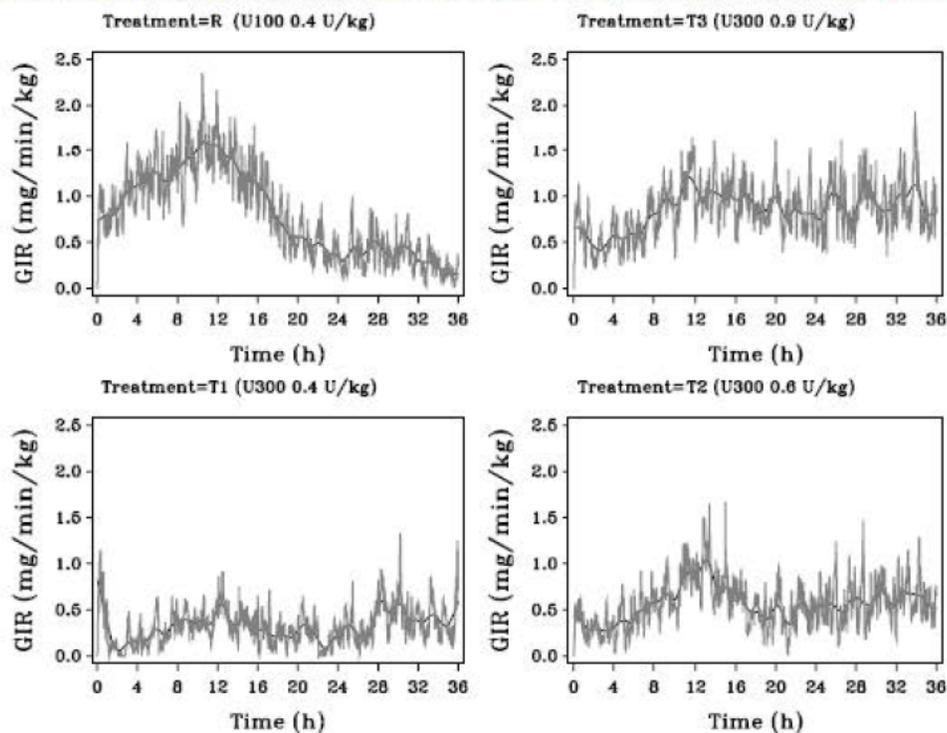
**Pharmacodynamics results:**

Mean smoothed body-weight-standardized glucose infusion rates (GIR) for insulin glargine U300 treatments (T<sub>1</sub> to T<sub>3</sub>) 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 T<sub>1</sub> to T<sub>3</sub> gained from T2H onwards to level at around T12H. Thereafter GIR T<sub>1</sub> to T<sub>3</sub> 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. T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub> denote injections of insulin glargine U300 (0.4, 0.6, and 0.9 U/kg respectively).

Total exogenous glucose consumption, GIR-AUC<sub>0-36</sub>, increased with U300 doses. Compared to R, GIR-AUC<sub>0-36</sub> was less under T<sub>1</sub> and T<sub>2</sub>, but greater under T<sub>3</sub> (see the table below).

Consistent with these findings, the T<sub>50%</sub>-GIR-AUC<sub>0-36</sub> median values were around 18 (17 to 19) hours for T<sub>1</sub> to T<sub>3</sub>, but 12 hours for R (see the table below).

Point estimates for GIR-AUC<sub>0-36</sub> ratios (90%CI) are: T<sub>1</sub>/R 0.12 (0.05 to 0.30), T<sub>2</sub>/R 0.33 (0.17 to 0.66) and T<sub>3</sub>/R 1.37 (0.89 to 2.13). In particular under T<sub>1</sub>, 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)**

|   | R<br>(U100 0.4 U/kg) | Test treatment        |                       |                       |
|---|----------------------|-----------------------|-----------------------|-----------------------|
|   |                      | T1<br>(U300 0.4 U/kg) | T2<br>(U300 0.6 U/kg) | T3<br>(U300 0.9 U/kg) |
| <b>GIR-AUC<sub>0-36</sub> (mg/kg)</b>             |                      |                       |                       |                       |
| 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        |
| <b>T<sub>50%</sub>-GIR-AUC<sub>0-36</sub> (h)</b> |                      |                       |                       |                       |
| 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).

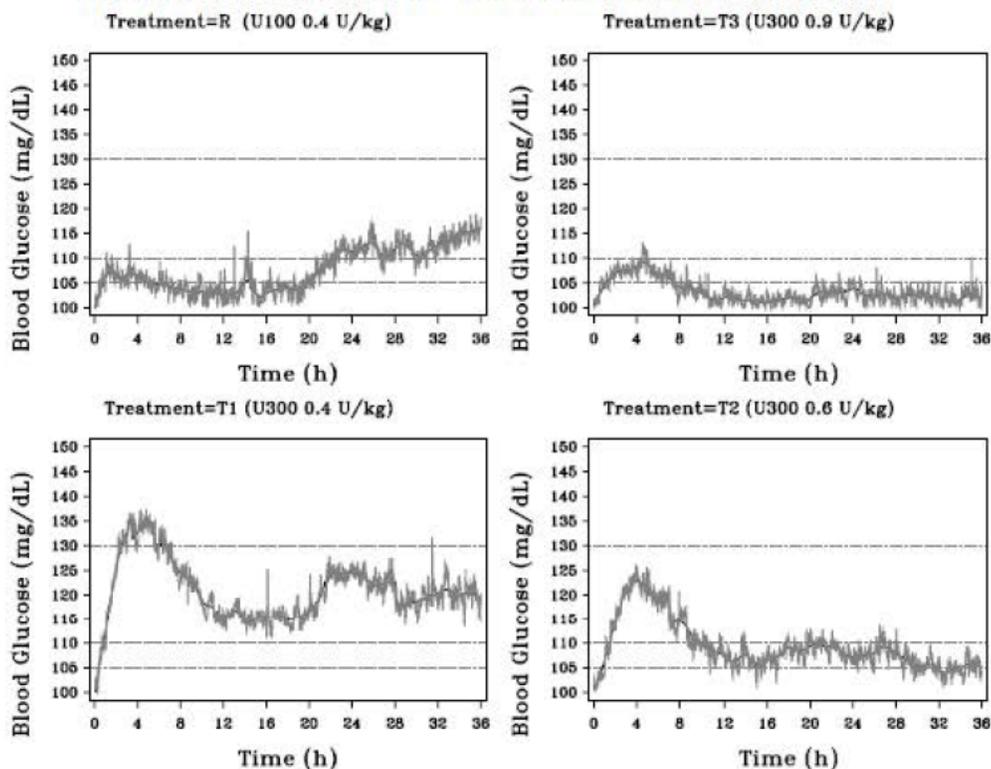
GIR-AUC values of zero were replaced by 1 mg/kg.

Similar to GIR, the shape of mean smoothed blood glucose (BG) profiles presented with compatible characteristics for all three test treatments T<sub>1</sub> to T<sub>3</sub>. 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 T<sub>1</sub> and T<sub>2</sub> BG values were above clamp level [5.6 mmol/L (100 mg/dL)] and the predefined level of euglycemia [5.8 mmol/L (105 mg/dL)], but T<sub>2</sub> BG was well within 5.8 – 6.1 mmol/L (105 - 110 mg/dL) limits and T<sub>1</sub> BG was within 6.1 – 7.2 mmol/L (110 - 130 mg/dL) limits.

Mean smoothed BG profiles for T<sub>3</sub> and R were similar until T20H with BG values between clamp level and predefined euglycemic level 5.8 – 6.1 mmol/L (105-110 mg/dL). After T20H, mean BG levels for R gradually increased to 6.4 mmol/L 115 mg/dL until clamp end, in line with the end-of-dose-phenomenon, while T<sub>3</sub> BG remained within the clamp and euglycaemic level limits 5.6 – 5.8 mmol/L (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:**

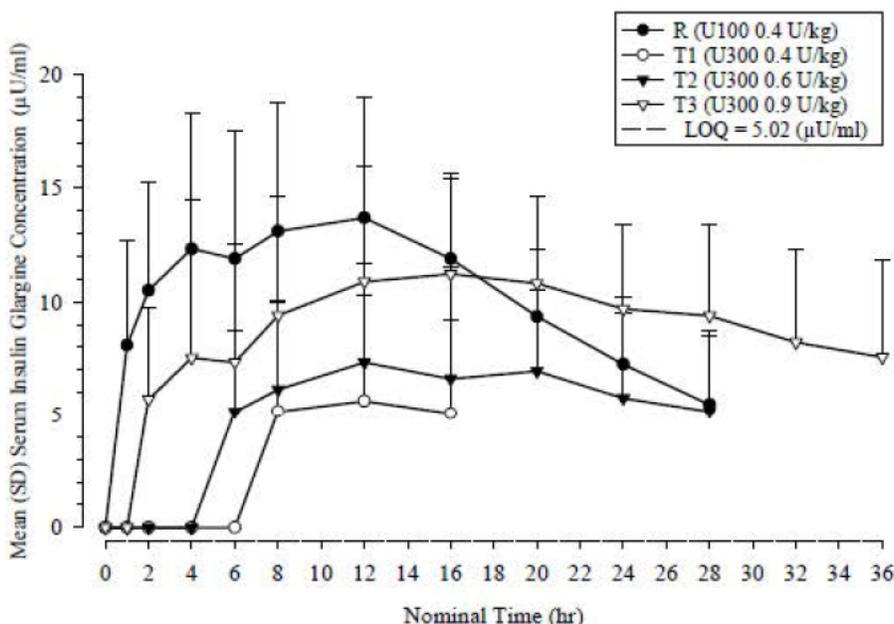
Two, 2 and 4 patients were reported to have a TEAE under R, T<sub>1</sub>, and T<sub>3</sub>, respectively. The most common TEAE was headache. One patient under T<sub>1</sub> had an episode of ventricular extrasystoles after dosing with intensity rated by the investigator as severe but with no relationship 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 T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>.

**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 (T<sub>1</sub>), 0.6 U/kg insulin glargine U300 (T<sub>2</sub>) and 0.9 U/kg insulin glargine U300 (T<sub>3</sub>) are presented in the figure below. Pharmacokinetic profiles for insulin glargine U300 treatments (T<sub>1</sub> to T<sub>3</sub>) 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 (T<sub>1</sub>), 0.6 U/kg (T<sub>2</sub>), and 0.9 U/kg (T<sub>3</sub>), 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 (T<sub>1</sub> to T<sub>3</sub>) 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 (T<sub>50%</sub>-INS-AUC<sub>0-36</sub>) was longer for patients receiving SC insulin glargine U300 doses (T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>) 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 T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>, respectively.

**Mean ± SD T<sub>50%</sub>-INS-AUC<sub>0-36</sub> 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. T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub> denote injections of insulin glargine U300 (0.4, 0.6, and 0.9 U/kg respectively).

The systemic mean exposure (INS-AUC<sub>0-36</sub>) 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-C<sub>max</sub> 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-C<sub>max</sub> for insulin glargine U300 0.9 U/kg (T3) was 13.0 µU/mL. The highest INS-C<sub>max</sub> of 15.3 µU/mL was observed for Lantus U100 0.4 U/kg.

Individual INS-T<sub>max</sub> 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<br>(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 <sup>b</sup>                      | 22                     | 15 <sup>c</sup>    | 20 <sup>d</sup>    | 22                 |
| INS-C <sub>max</sub>                | 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 <sub>max</sub> <sup>a</sup>   | 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 <sub>0-36</sub>             | 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 <sub>0-24</sub>             | 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]       |

<sup>a</sup> Median (Min - Max)

<sup>b</sup> Subjects 3 and 13 excluded from PK population (study discontinuation in period 1).

<sup>c</sup> 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.

<sup>d</sup> 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-C<sub>max</sub>) 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<sub>0-24</sub> (90%CI) were 0.59 for the comparison T1/R, 0.49 for T2/R, and 0.84 for T3/R.

**Conclusions:**

Pharmacodynamics: Insulin glargine U300 time profiles for GIR, BG, and PK were consistent during the clamp period, with higher insulin concentrations correlating to higher GIR and lower BG levels. These findings suggest a close PK/PD relationship.

Profiles of GIR, BG and PK for T<sub>1</sub> to T<sub>3</sub> were different from R (Lantus U100). GIR for R continuously increased until T12H and then declined until clamp end, which is consistent with the observation of BG values at the euglycemic level early during the clamp which then increased until clamp end. By contrast, insulin glargine U300 treatments showed a later GIR peak and generally sustained pharmacodynamic effects for the 36 hours of the clamp, most evident with T<sub>2</sub> and T<sub>3</sub>.

Due to the predefined clamp end at T36H, the full duration of insulin glargine U300 activity could not be assessed, and there could be glucose-lowering activity beyond 36 hours post dose.

Treatment with T<sub>1</sub> and T<sub>2</sub> required an overall lower amount of exogenously administered glucose (expressed as GIR-AUC<sub>0-36</sub>) compared to R, while under T<sub>3</sub> GIR-AUC<sub>0-36</sub> was greater than under R. The GIR and GIR-AUC should be, however, viewed in the context of BG levels. The euglycemic BG levels observed with R and T<sub>3</sub> were achieved at the expense of a greater GIR and hence greater GIR-AUC. Under fasting nonclamp conditions without continuous glucose infusion, R and T<sub>3</sub> could have lowered BG to hypoglycemic levels. By contrast, under T<sub>1</sub> and T<sub>2</sub>, after an initial period of suboptimally controlled BG levels, reflecting the time needed for T<sub>1</sub> and T<sub>2</sub> to take effect, BG stabilized at mean levels slightly above the euglycemic threshold at a low GIR.

Safety: All treatments were well tolerated with no differences in safety-related parameters between treatments.

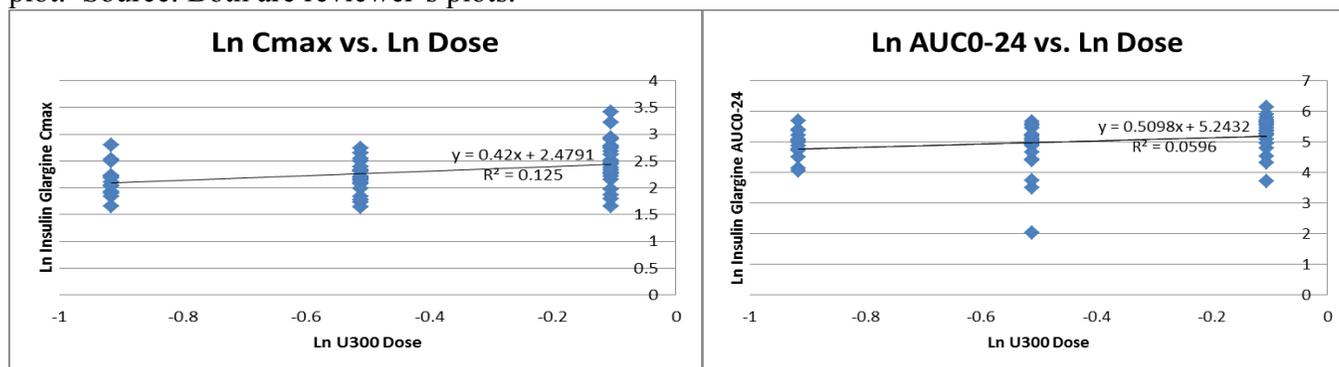
Pharmacokinetics: Pharmacokinetic profiles for insulin glargine U300 treatments (T<sub>1</sub> to T<sub>3</sub>) were flat between 8 and 16 hours, 6 and 28 hours, and over the 36 hours observation period for the U300 doses 0.4 U/kg (T<sub>1</sub>), 0.6 U/kg (T<sub>2</sub>), and 0.9 U/kg (T<sub>3</sub>), 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.

The overall flatter profile of the T<sub>1</sub> to T<sub>3</sub>, compared to R was also reflected in the times to reach 50% of the exposure (median T<sub>50%-INS-AUC<sub>0-36</sub></sub>) being about 15, 17, and 19 hours for T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>, respectively, and about 13 hours for R.

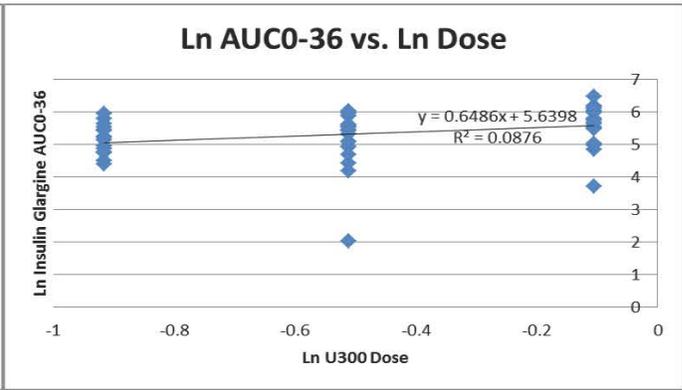
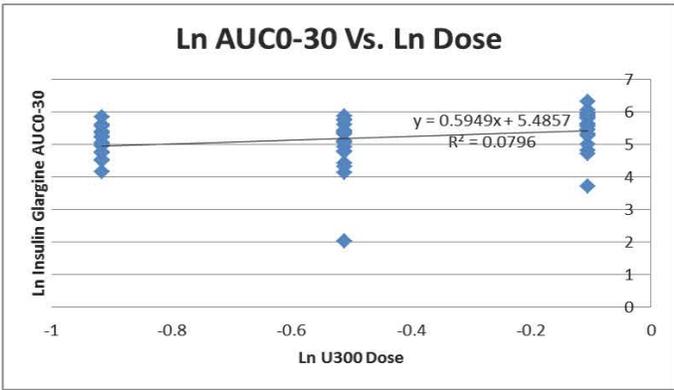
The systemic exposure increased with the insulin glargine U300 doses. Compared to R, the exposure over the clamp period of 36 hours (INS-AUC<sub>0-36</sub>) was significantly lower for T<sub>1</sub> and T<sub>2</sub> and similar for T<sub>3</sub>.

**Date of report:** 18-Oct-2013

The ln insulin glargine C<sub>max</sub> vs. ln U300 dose plot and ln insulin glargine AUC<sub>0-24 hours</sub> vs. ln U300 dose plot. Source: Both are reviewer's plots.



The ln insulin glargine AUC<sub>0-30 hours</sub> vs. ln U300 dose plot and ln insulin glargine AUC<sub>0-36 hours</sub> vs. ln U300 dose plot. Source: Both are reviewer's plots.



## Multiple Dose PKPD:

Clinical Study Report  
HOE901-U300 - TDR11626 - insulin glargine

18-Oct-2013  
Version Number: 3 (electronic 3.0)

## SYNOPSIS

|  |
|--|
| <b>Title of the study:</b> 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<br><b>Study number:</b> TDR11626 |
| <b>Investigator(s):</b> Dr. Thomas Jax, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, 41460 Neuss, Germany  |
| <b>Study center(s):</b> One center in Germany  |
| <b>Publications (reference):</b> None  |
| <b>Study period:</b><br>Date first patient enrolled: 28 March 2011<br>Date last patient completed: 28 May 2011   |
| <b>Phase of development:</b> Phase 1 (exploratory)   |
| <b>Objectives:</b> <ul style="list-style-type: none"><li>To assess the safety and tolerability of two dose levels of HOE901-U300 in a once-daily multiple dosing regimen</li><li>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</li></ul>   |
| <b>Methodology:</b> 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).  |
| <b>Number of patients:</b><br>Planned: 30<br>Randomized: 30<br>Treated: 30<br><br><b>Evaluated:</b><br>Pharmacodynamic: 30<br>Safety: 30<br>Pharmacokinetics: 30   |
| <b>Diagnosis and criteria for inclusion:</b> Male or female patients aged 18 to 65 years with diabetes mellitus type 1 (T1DM) for more than one year.  |
| <b>Investigational (test [T]) product:</b> Insulin glargine solution for injection 300 U/mL (HOE901-U300).<br><b>Dose:</b> 0.4 U/kg (Test 1 [T1] treatment) in Cohort 1; 0.6 U/kg (T2 treatment) in Cohort 2<br><b>Administration:</b> Once daily (QD), 8 days in one treatment period (TP), subcutaneously (SC), periumbilically.<br><b>Batch number(s):</b> C1011129   |

**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)

**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.

**Batch number(s):** 0F999A

**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<sub>0-24</sub> [mg/kg]);
- Area under the body weight standardized GIR time curve up to 36 h after dosing (GIR-AUC<sub>0-36</sub> [mg/kg]);
- Time (h) to 50% of GIR-AUC<sub>0-24</sub> (T50%-GIR-AUC<sub>0-24</sub> [h]);
- Time (h) to 50% of GIR-AUC<sub>0-36</sub> (T50%-GIR-AUC<sub>0-36</sub> [h]);
- Maximum smoothed body weight standardized GIR (GIR<sub>max</sub> [mg\*min/kg]);
- First time after dosing to reach GIR<sub>max</sub> (GIR-T<sub>max</sub> [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 5.8 mmol/L (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 6.1 mmol/L, 7.2 mmol/L, or 8.3 mmol/L (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<sub>max</sub>);
- First time to reach INS-C<sub>max</sub> (INS-T<sub>max</sub>);
- 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<sub>0-24</sub>);
- 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<sub>0-36</sub>);
- Time to 50% of INS-AUC<sub>0-24</sub> (T<sub>50%</sub>-INS- AUC<sub>0-24</sub>);
- Time to 50% of INS-AUC<sub>0-36</sub> (T<sub>50%</sub>-INS- AUC<sub>0-36</sub>).

**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  $\mu\text{U/mL}$ .

**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  $\text{GIR-AUC}_{0-24}$ ,  $\text{GIR-AUC}_{0-36}$ , and  $\text{GIR}_{\text{max}}$  (using a linear mixed effects model for log transformed data by cohort); treatment differences T1-R and T2-R for  $\text{T50\%-GIR-AUC}_{0-24}$ ,  $\text{T50\%-GIR-AUC}_{0-36}$ ,  $\text{GIR-}t_{\text{max}}$ , 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).

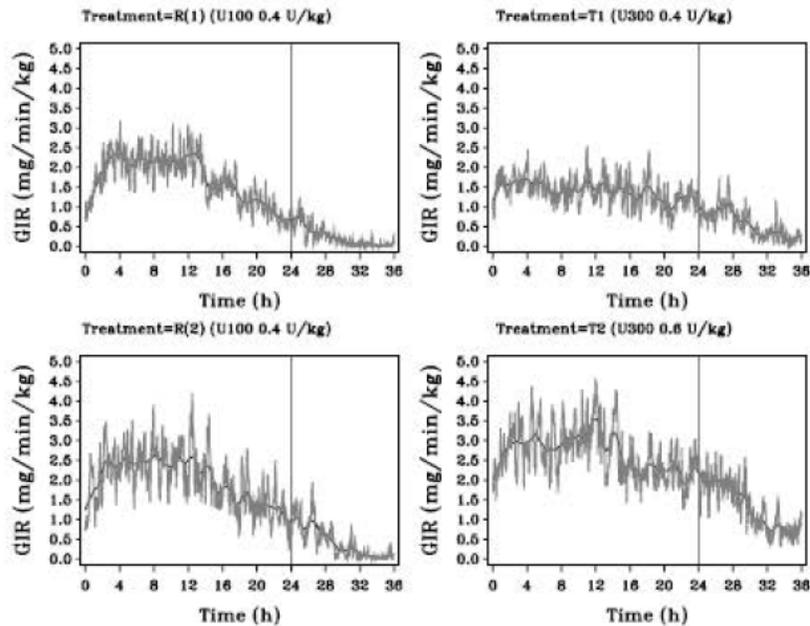
**Pharmacokinetics:** PK parameters were summarized by cohort and treatment, and additionally for treatment R pooled over Cohorts 1 and 2, using descriptive statistics. Statistical analyses were provided separately for each cohort and compared test treatments (T1 or T2) with reference treatment (R) of 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  $\text{INS-AUC}_{0-24}$ ,  $\text{INS-AUC}_{0-36}$ , and  $\text{INS-C}_{\text{max}}$  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  $\text{T50\%-INS-AUC}_{0-36}$  and  $\text{T50\%-INS-AUC}_{0-24}$  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<sub>max</sub> 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(0-24h) and GIR-smFL(0-36h)) 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 6.1, 7.2 and 8.3 mmol/L (110, 130 and 150 mg/dL), as well as at or below the level of euglycemia  $\leq 5.8$  mmol/L ( $\leq 105$  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 6.1, 7.2 and 8.3 mmol/L (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 13.9 mmol/L (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. Cardiac 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.

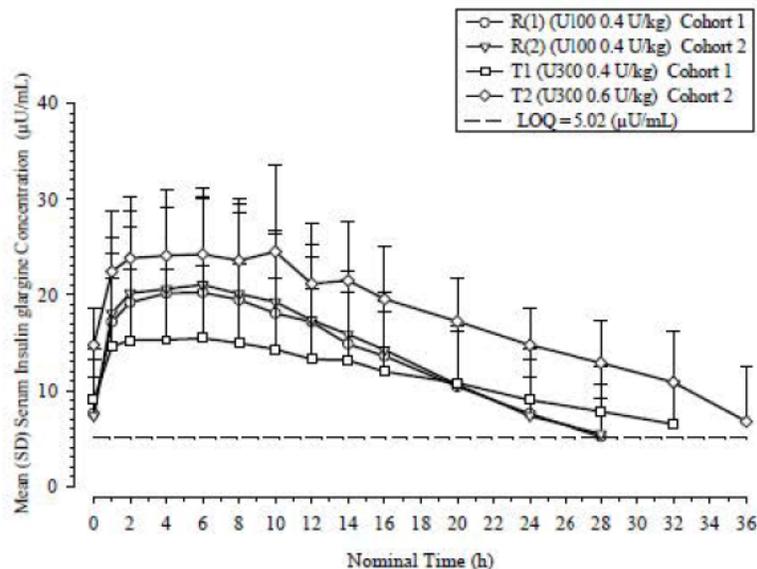
There were 2 events of severe hypoglycemia in two patients, which both occurred under HOE901-U300. These 2 events were nocturnal and both occurred in the first half of the respective TP: One on about 6 hours after dosing of Day 4 under 0.4 U/kg HOE901-U300 and the other at about 9 hours after dosing 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 to 16 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.

### Conclusions:

At steady state following 8 days of QD dosing in patients with T1DM, insulin glargine given as HOE901-U300 displayed a flatter, more evenly balanced activity profile of extended duration as compared to Lantus U100. The overall PD effects, as assessed by GIR-AUC, were comparable over the entire clamp period of 36 hours, but were lower within the first 24 hours of the clamp period following administration of 0.4 U/kg HOE901-U300 as compared to the same dose of Lantus U100. The overall PD effects over 24 and 36 hours of 0.6 U/kg HOE901-U300 were somewhat greater than those of 0.4 U/kg Lantus U100.

Both dose levels of HOE901-U300 (0.4 and 0.6 U/kg) as well as 0.4 U/kg Lantus U100 were well tolerated in this 8-day QD dosing regimen. There were no SAEs and no deaths in the 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 under 0.4 U/kg HOE901-U300 (64.7%).

Overall, the percentages of patients affected by hypoglycemia were comparable between all 3 treatments, but the number of events in relation to the number of patients per treatment for 0.4 U/kg HOE901-U300 (T1) was lower (5.2; 16 out of 17 [94.1%] patients had 88 events) whereas for 0.6 U/kg HOE901-U300 (T2) higher (8; 12 [100%] patients had 96 events) than under 0.4 U/kg Lantus U100 (R) (6.3; 29 out of 30 [96.7%] patients had 188 events). Hypoglycemia was reported as a TEAE in 11 (64.7%) patients under T1, 10 (83.3%) patients under T2, and 23 (76.7%) patients under R.

There were 2 events of severe hypoglycemia in 2 patients administered HOE901-U300. Both events were nocturnal and occurred in the first half of the respective TP: one at about 6 hours after dosing of Day 4 with 0.4 U/kg HOE901-U300, and the other at about 9 hours after dosing of Day 2 with 0.6 U/kg HOE901-U300. However, the percentage of patients affected by nocturnal hypoglycemia was generally lower with 0.4 U/kg HOE901-U300 (58.8%) than with 0.4 U/kg Lantus U100 (86.7%) or with 0.6 U/kg HOE901-U300 (83.3%).

The antiinsulin antibody status, titer, binding, and cross-reactivity did not change significantly throughout the course of the study and did not differ significantly between the two treatment cohorts.

The steady state serum insulin profiles corroborate the PD findings. HOE901-U300 displayed a flatter and more constant serum profile as compared to Lantus U100, particularly over the 24 hours of the dosing interval. The serum concentration profiles of the HOE901-U300 treatments T1 (0.4 U/kg) and T2 (0.6 U/kg) showed quantifiable exposure until 32 and 36 hours post dose, respectively.

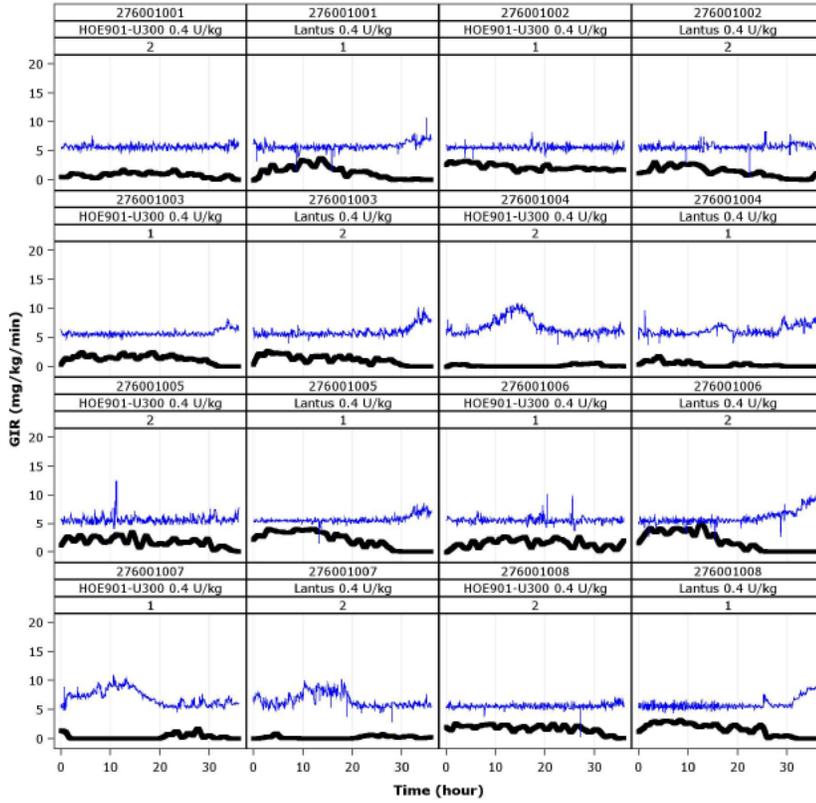
Exposure to insulin glargine was slightly lower within 24 hours with HOE901-U300 than with Lantus U100 for the dose of 0.4 U/kg, but was about the same within 36 hours. The higher dose of 0.6 U/kg HOE901-U300 produced a correspondingly greater exposure with an otherwise similar concentration time profile. The time to reach 50% of the exposure over 24 hours (T50%-INS-AUC<sub>0-24</sub>) was similar for all treatments, but was longer for the HOE-U300 treatments compared to the Lantus U100 reference over 36 hours after dosing (T50%-INS-AUC<sub>0-36</sub>).

Determination by LC-MS/MS of immunoaffinity-enriched metabolites from plasma confirmed equal metabolism of insulin glargine regardless of formulation, with the main metabolite being 21A-Gly-human insulin, defined as M1.

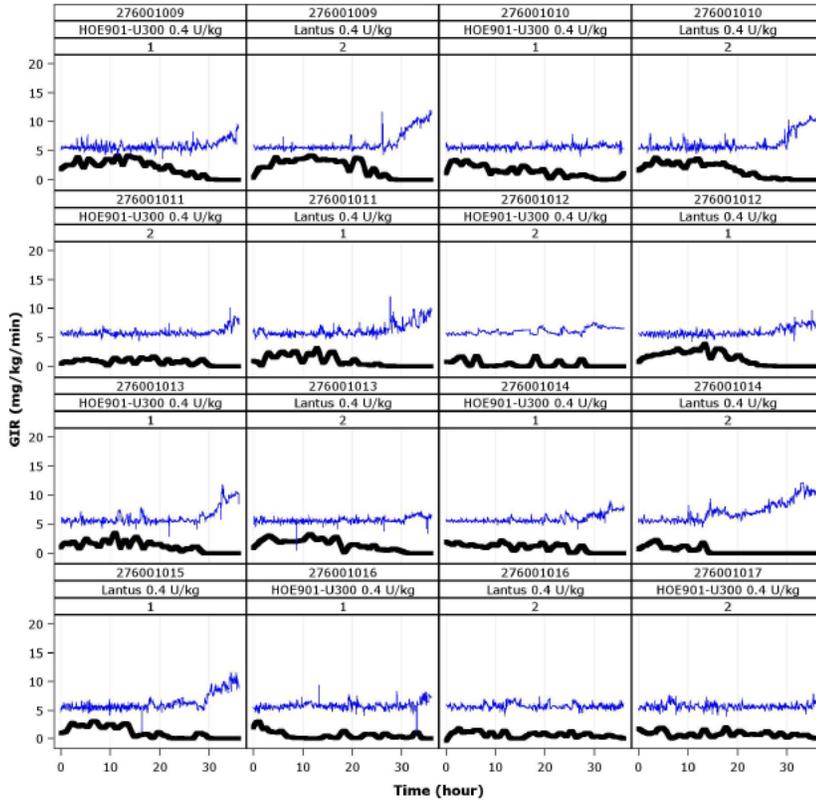
**Date of report:** 18-Oct-2013

This reviewer checked the validity of the euglycemic clamp via plotting the smoothed body-weight adjusted GIR (**blue thin line**) and BG concentrations (**black thicker line**). Subject 276001007 showed close to 0 GIR for the initial 20 hours, which may reflect uncontrollable BG concentrations, for both 0.4 U/kg U300 and 0.4 U/kg U100 dose groups. Subject 276001004 also showed close to 0 GIR for the initial 20 plus hours for the 0.4 U/kg U300 dose group. Overall, this check showed the euglycemic clamp was working properly.

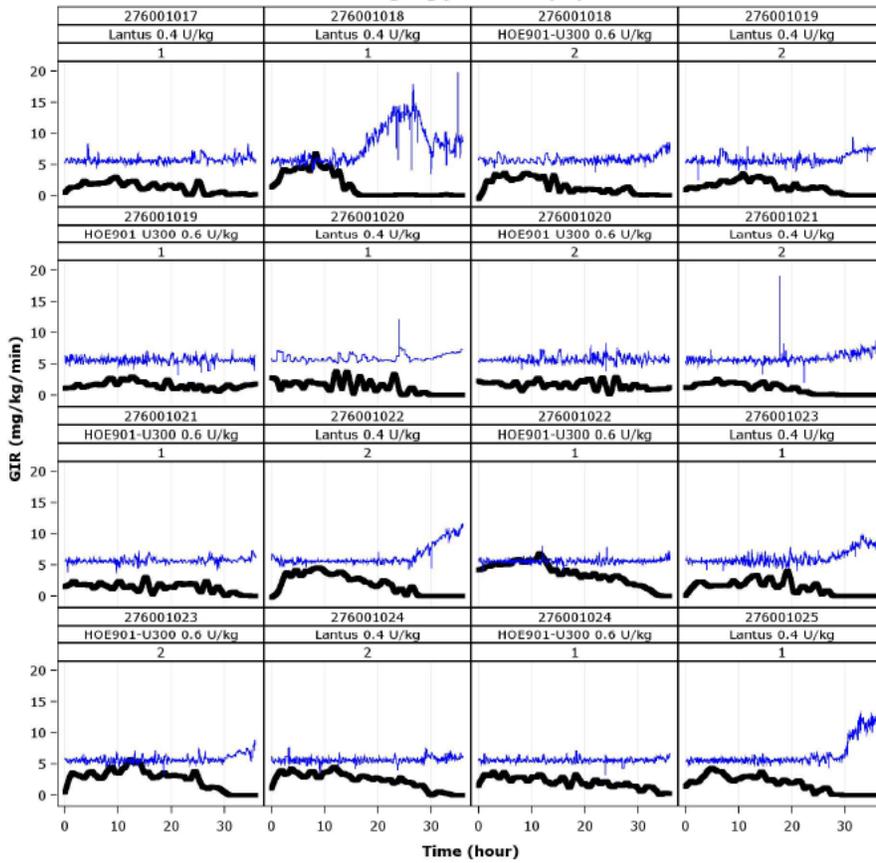
Smoothed GIR during euglycemic clamp by treatment



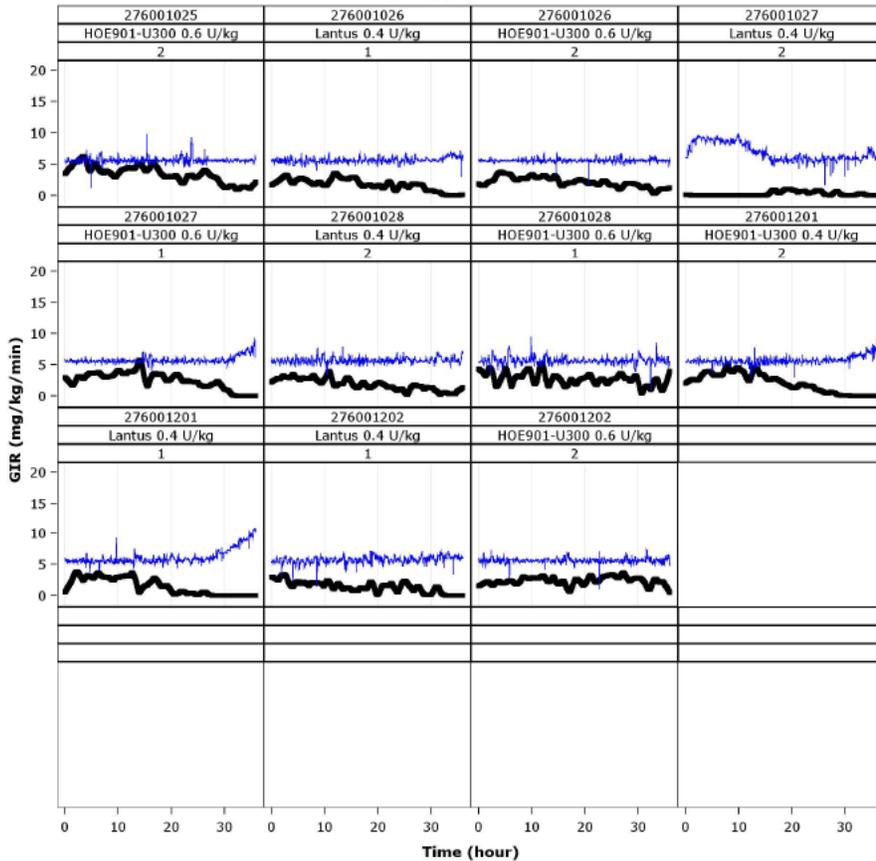
Smoothed GIR during euglycemic clamp by treatment



Smoothed GIR during euglycemic clamp by treatment



Smoothed GIR during euglycemic clamp by treatment



Study

TDR11626's report, Page 155/162 shows that the mean terminal half-life of M1 is 21.2 – 24.2 hours in Table 47. This M1 terminal half-life estimation is via the LC-MS/MS bioanalytical assay, which is more specific for M1.

## Single Dose PKPD PKD10086:

Clinical Study Report  
HOE901 - PKD10086

22-Oct-2013  
Version number: 2

### Criteria for evaluation:

#### Pharmacodynamic

*Primary:* area under the glucose infusion rate (GIR)-time curve within 24 hours (GIR-AUC<sub>(0-24h)</sub> [mg/ kg])

*Secondary:* time to 50% GIR-AUC<sub>(0-24h)</sub> (T50%-GIR-AUC<sub>(0-24h)</sub> [h])

**Safety:** adverse events reported by subject or noted by Investigator; standard clinical laboratory (biochemistry, hematology); vital signs and electrocardiogram

#### Pharmacokinetics:

*Primary:* area under the serum insulin glargine concentration-time curve: (INS-AUC<sub>(0-24h)</sub> [ $\mu\text{U h mL}^{-1}$ ])

*Secondary:* time to 50% INS-AUC<sub>(0-24h)</sub> (T50%-INS-AUC<sub>(0-24h)</sub> [h])

### Pharmacokinetic sampling times and bioanalytical methods:

Serum insulin glargine and C-peptide concentrations were determined from samples collected 1 hour, 30 minutes, and immediately prior to injection of study medication and at 30 minutes; 1 and 2 hours; bihourly up to 24 hours; and 30 hours after injection. Concentrations were determined using radioimmunoassay methods with a lower limit of quantification of 5.02  $\mu\text{U/mL}$  for insulin glargine and 0.300 ng/mL for serum C-peptide.

### Statistical methods:

#### Pharmacodynamics

Relative bioefficacy (activity) was estimated for GIR-AUC<sub>(0-24h)</sub> using a mixed effects model to analyze the untransformed parameter, with fixed terms for sequence, period, and formulation; random terms for subject within sequence; and formulation-specific between-subject and within-subject variances and subject-by-formulation variance. Point estimates and 90% confidence intervals (CI) for the formulation ratio were obtained using Fieller's theorem. Equivalent bioefficacy was to be concluded if the CI for the formulation ratio was within the interval [0.80 to 1.25].

#### Safety

Evaluation was based on review of individual values and descriptive statistics. The number and percentage of subjects with at least 1 treatment-emergent adverse event (TEAE) are summarized and/or listed by treatment, system organ class, and preferred term for TEAEs, serious TEAEs, and discontinuations due to TEAEs (MedDRA version 10.0). Abnormalities in biochemistry and hematology parameters, vital signs, and electrocardiogram parameters were assessed using potentially clinically significant abnormality (PCSA) criteria, and subjects with on-treatment PCSAs are summarized and listed.

#### Pharmacokinetics

Relative bioavailability for INS-AUC<sub>(0-24h)</sub> was analyzed using a mixed effects model for the log-transformed parameter, with fixed terms for sequence, period, and formulation; random terms for subject within sequence; and formulation-specific between-subject and within-subject variances and subject-by-formulation variance. Point estimates and 90% CIs for the difference between formulation means were obtained within the mixed effects model framework then converted to the ratio scale using the antilog transformation. Equivalent bioavailability was to be concluded if the CI for the formulation ratio was within the interval (0.80 to 1.25).

### Summary:

#### Pharmacodynamic results:

Bioactivity of insulin glargine after injection from the test formulation as measured by the glucose infusion rate was 39.4% lower than that after injection from the reference formulation. Confidence intervals for the mean ratio test/ reference were outside the conventional bioequivalence acceptance interval of 0.80 to 1.25 for the 0- to 24-hour clamp (90% CI: 0.532 to 0.709) and for all other clamp time periods analyzed (0 to 30 hours, 4 to 20 hours, 12 to 24 hours).

The time to 50% of GIR-AUC was greater for the test formulation than for the reference formulation by 0.545 (90% CI: 0.157 to 1.030) hours for the 0 to 24-hour clamp.

*Safety results:*

Treatment with the test formulation was safe and well tolerated. No deaths or serious adverse events were reported during the study, and there were no discontinuations due to an adverse event. Headache was the most commonly reported adverse event and was reported at similar frequencies for both test and reference formulations. None of the adverse events were rated as severe. No signs of local intolerance were noted.

PCsAs were observed in hemoglobin values but none were clinically significant and no corresponding adverse events were reported. No subjects had prolonged QTc intervals ( $\geq 500$  ms) or QTc changes greater than 60 ms.

*Pharmacokinetic results:*

Exposure to insulin glargine after injection from the test formulation as determined by INS-AUC for the 0-to-24-hour clamp was 38.5% lower than that from the reference formulation. The confidence interval for the mean ratio test/reference was outside the conventional bioequivalence acceptance interval of 0.80 to 1.25 for the 0- to 24-hour clamp (90% CI: 0.574 to 0.659) and for all other clamp periods analyzed (0 to 30 hours, 4 to 20 hours, 12 to 24 hours).

The time to 50% of INS-AUC at 0 to 24 hours was higher for the test formulation than for the reference formulation but the difference was not statistically significant (90% CI: -0.176 to 0.535).

*Conclusions:* Bioequivalence of Lantus U300 and Lantus U100 was not established.

**Date of report:** 22-Oct-2013

This reviewer used the following equations to calculate the intra-subject variability of U300 and U100 for the duplicate administration of U300 and U100:

With  $n$  being the number of data pairs and  $x_1$  and  $x_2$  duplicate measurements, the SD, Mean and CV are given by:

$$SD = \sqrt{\frac{\sum (x_1 - x_2)^2}{2n}}$$

$$Mean = \frac{\sum (x_1 + x_2)}{2n}$$

$$CV(\%) = 100 \times \frac{SD}{Mean}$$

Coefficient of variation from duplicate measurements in this website:

<http://www.medcalc.org/manual/cvfromduplicates.php>

## Single Dose PKPD PKD13560:

Clinical Study Report  
HOE901-PKD13560 - insulin glargine

20-FEB-2014  
Version number: 2

### SYNOPSIS

|  |  |
|--|--|
| <b>Title of the study:</b> 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   |  |
| <b>Study number:</b> PKD13560  |  |
| <b>Investigator(s):</b> Dr. Christoph KAPITZA, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9, 41460 Neuss, Germany   |  |
| <b>Study center(s):</b> One center in Germany  |  |
| <b>Publications (reference):</b> None  |  |
| <b>Study period:</b><br>Date first subject enrolled: 16 April 2013<br>Date last subject completed: 05 August 2013  |  |
| <b>Phase of development:</b> 1   |  |
| <b>Objectives:</b><br>Primary objective: <ul style="list-style-type: none"><li>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</li></ul> Secondary objectives: <ul style="list-style-type: none"><li>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</li><li>To assess the safety and tolerability of the test and reference formulations of HOE901-U300</li></ul> |  |
| <b>Methodology:</b> Randomized (1:1), double-blind, 2-treatment, 2-period, 2-sequence, crossover, multiple (6-day once-daily) dosing regimen, single-center study  |  |
| <b>Number of subjects:</b>   | Planned: 50<br>Randomized: 50<br>Treated: 50               |
| <b>Evaluated:</b>  | Pharmacodynamics: 50<br>Safety: 50<br>Pharmacokinetics: 50 |
| <b>Diagnosis and criteria for inclusion:</b> Male or female patients aged 18 to 64 years with diabetes mellitus type 1 (T1DM) for more than 1 year. Main inclusion criteria: HbA <sub>1c</sub> ≤9%; total insulin dose of <1.2 U/kg/day.   |  |
| <b>Study treatments</b><br><b>Investigational medicinal product:</b> Insulin glargine solution for injection 300 U/mL (HOE901-U300)  |  |
| <b>Formulations:</b> <ul style="list-style-type: none"><li>Test formulation (treatment T): contains (b) (4) (supplied in (b) (4))</li><li>Reference formulation (treatment R): (b) (4) (supplied in cartridges (b) (4))</li></ul>  |  |
| <b>Route(s) of administration:</b> SC, periumbilical   |  |
| <b>Dose regimen:</b> 0.4 U/kg/day  |  |
| <b>Batch number(s):</b> C1027161 (T), C1022774 (R)   |  |
| <b>Duration of treatment:</b> 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 of 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 GIR versus time curve within 24 hours after dosing on Day 6 during the clamp (GIR-AUC<sub>0-24</sub> [mg/kg])

The following additional secondary PD variables were derived:

- Time to reach at least 50% of the GIR-AUC<sub>0-24</sub> (T<sub>50%</sub>-GIR-AUC<sub>0-24</sub> [hours])
- Maximum smoothed body weight standardized GIR (GIR<sub>max</sub> [mg/kg/min])
- Time to reach GIR<sub>max</sub> (GIR-T<sub>max</sub> [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<sub>max</sub> and the time to GIR<sub>max</sub> 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<sub>0-24</sub>)

Secondary PK variables:

- Maximum serum concentration observed (INS-C<sub>max</sub>)
- First time to reach INS-C<sub>max</sub> (INS-T<sub>max</sub>)
- Time to reach 50% of INS-AUC<sub>0-24</sub> (T<sub>50%</sub>-INS-AUC<sub>0-24</sub>)

**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 IMP administration and/or PD measurements and whose PD parameters were available and evaluable. Pharmacodynamic 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<sub>0-24</sub>, as well as for GIR<sub>max</sub>, 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<sub>0-24</sub> and GIR<sub>max</sub>. Time to 50% of GIR-AUC<sub>0-24</sub> (T<sub>50%</sub>-GIR-AUC<sub>0-24</sub>) 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 (PCSA) 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 whom 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 BMI was 25.38 kg/m<sup>2</sup>. 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<sub>0-24</sub>, GIR<sub>max</sub> and GIR-T<sub>max</sub> by treatment are provided in the table below.

**Descriptive statistics for GIR-AUC<sub>0-24</sub>, GIR<sub>max</sub> and GIR-T<sub>max</sub>**

|                                       | T (U300 + polysorbate) | R (U300)          |
|---------------------------------------|------------------------|-------------------|
| <b>GIR-AUC<sub>0-24</sub> (mg/kg)</b> |                        |                   |
| 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    |
| <b>GIR<sub>max</sub> (mg/kg/min)</b>  |                        |                   |
| 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         |
| <b>GIR-T<sub>max</sub> (h)</b>        |                        |                   |
| 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

GIR<sub>max</sub> and GIR-T<sub>max</sub> are based on smoothed GIR profiles (LOESS, factor 0.06).

Q1 and Q3 denote first and third quartiles

PGM=PRODOPS/HOE901/PKD13560/CSR/REPORT/PGM/pd\_descgir\_d\_1.sas OUT=REPORT/OUTPUT/pd\_descgir\_d\_1.rtf (13SEP2013 - 16:48)

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<sub>0-24</sub>). The GIR-AUC<sub>0-24</sub> and the maximum glucose infusion rate (GIR<sub>max</sub>) 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<sub>0-24</sub> and GIR<sub>max</sub> - pharmacodynamic population**  
**Point estimates of treatment ratio with 90 % confidence intervals**

| Treatment ratio             | Parameter                       | Estimate | 90% CI         |
|-----------------------------|---------------------------------|----------|----------------|
| T (U300 (b) (4) / R (U300)) | GIR-AUC <sub>0-24</sub> [mg/kg] | 1.02     | (0.87 to 1.20) |
|                             | GIR <sub>max</sub> [mg/kg/min]  | 0.96     | (0.87 to 1.06) |

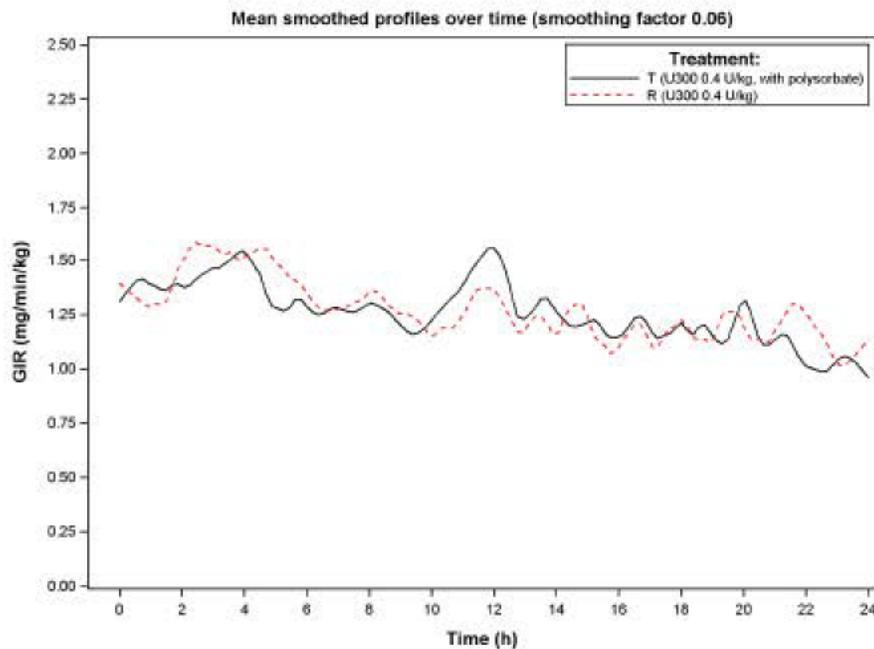
GIR denotes body weight standardized glucose infusion rate

GIR<sub>max</sub> is based on individually smoothed profiles, LOESS, factor 0.06.

PGM=PRODOPS/HOE901/PKD13560/CSR/REPORT/PGM/pd\_ratio.sas OUT=REPORT/OUTPUT/pd\_ratio\_ra\_k\_1\_2.rtf (13SEP2013 - 21:26)

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  
 PGM=PRODOPS/HOE901/PKD13560/CSR/REPORT/PGM/pd\_igimeanover\_d\_g.sas OUT=REPORT/OUTPUT/pd\_igimeanover\_d\_g\_006\_i.rtf  
 (13SEP2013 - 16:53)

Consistent with the evenly balanced GIR profiles, the  $T_{50\%}$ -GIR-AUC<sub>0-24</sub> 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<sub>0-24</sub>

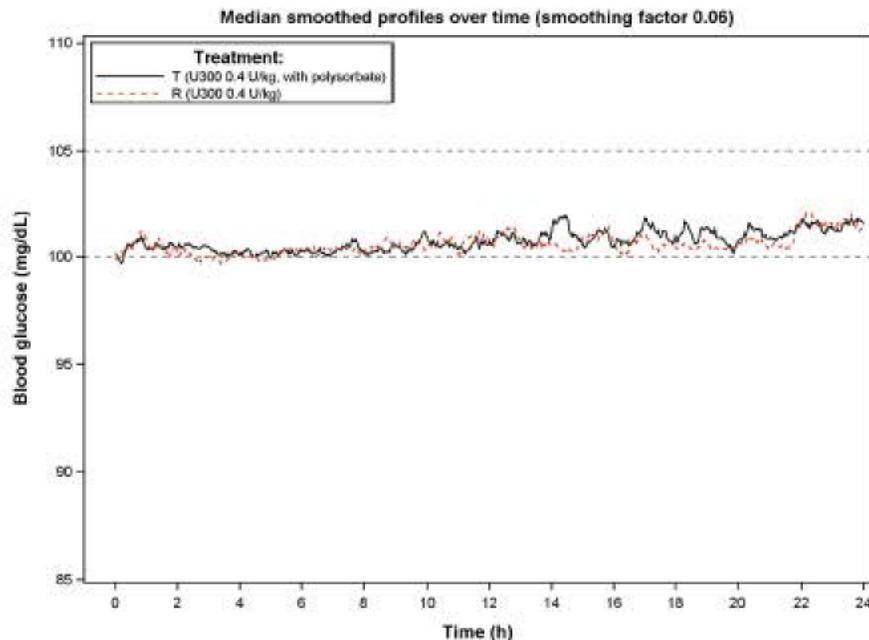
|  | T (U300 + polysorbate) | R (U300)       |
|--|------------------------|----------------|
| $T_{50\%}$ GIR-AUC <sub>0-24</sub> (h) |                        |                |
| Number                                 | 50                     | 50             |
| Mean (SD)                              | 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  
 PGM=PRODOPS/HOE901/PKD13560/CSR/REPORT/PGM/pd\_idescgauc\_d\_t.sas OUT=REPORT/OUTPUT/pd\_idescgauc\_d\_t\_i.rtf  
 (13SEP2013 - 16:49)

The time to 50% of GIR-AUC<sub>0-24</sub> 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<sub>0-24</sub> did not indicate either any relevant differences between treatment T and 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

PGM=PROCOP5.HOE901.PKD13560.CSR.REPORT/PGM/pd\_bgmedover\_d\_g.sas OUT=REPORT/OUTPUT/pd\_bgmedover\_d\_g\_006\_i.rtf (18SEP2013 - 8:26)

Equivalent glucose disposal (bio-equipotency) was demonstrated for HOE901-U300 (b) (4), (treatment T) and (b) (4), (treatment R) as attested by 90% CIs for the treatment ratios T/R for  $GIR_{AUC_{0-24}}$  and  $GIR_{min}$  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%).

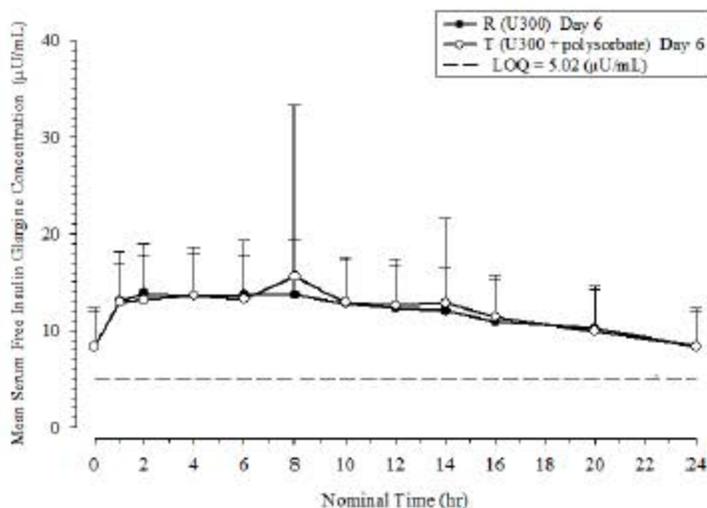
There were only few PCSA findings in clinical chemistry and vital signs, which were without clinical relevance and with no differences between treatments. There were few PCSAs for ECG parameters and without preference for either formulation. No ECG abnormalities were classified as clinically relevant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



Source = PKS Study : PKD13560; Scenario: S-D-A-EV-OD, Version 7  
Date/Time = 9/12/2013 1:01:15 PM

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

Pharmacokinetic data for insulin glargine by treatment

| Mean ± SD<br>(Geometric Mean) [CV%]  | Free Insulin Glargine in Serum |                              |
|--------------------------------------|--------------------------------|------------------------------|
|                                      | T (U300 + polysorbate)         | R (U300)                     |
|                                      | Day 6                          | Day 6                        |
| N                                    | 50                             | 49                           |
| INS-C <sub>24h</sub><br>[µU/ml]      | 18.6 ± 18.7<br>(15.8) [100.8]  | 16.6 ± 5.92<br>(15.6) [35.7] |
| INS-t <sub>1/2α</sub> *<br>[h]       | 4.04<br>(1.00 - 16.00)         | 6.00<br>(1.00 - 24.00)       |
| INS-AUC <sub>0-24</sub><br>[µU·h/ml] | 289 ± 107<br>(270) [36.9]      | 290 ± 93.5<br>(273) [32.3]   |

\* Median (Min - Max)

Source = PKS Study : PKD13560; Scenario: S-D-A-EV-OD, Version 7

**Pharmacokinetic data for insulin glargine by treatment (T<sub>50%</sub> of INS-AUC<sub>0-24</sub>)**

|                   | T (U300 (b) (4)) | 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    |

PGM=PRODOPS/HOE901/PKD13560/CSR/REPORT/PGM/pk\_descinsauc\_k\_1.sas  
 OUT=REPORT/OUTPUT/pk\_descinsauc\_k\_1.rtf (30SEP2013 - 16:26)

Equivalence in bioavailability (bioequivalence) was demonstrated for HOE901-U300 (b) (4) (treatment T) and (b) (4) (treatment R) as attested by 90% CIs for the treatment ratios T/R for INS-AUC<sub>0-24</sub> and INS-C<sub>max</sub> resting within the 0.80 to 1.25 acceptance range.

**Treatment ratio for INS-AUC<sub>0-24</sub> and INS-C<sub>max</sub> with 90% confidence intervals**

| Treatment ratio             | Parameter             | Estimate | 90% CI         |
|-----------------------------|-----------------------|----------|----------------|
| T (U300 (b) (4)) / R (U300) | INS-AUC0-24 (µU.h/mL) | 1.00     | (0.95 to 1.05) |
|                             | INS-Cmax (µU/mL)      | 1.02     | (0.91 to 1.14) |

PGM=PRODOPS/HOE901/PKD13560/CSR/REPORT/PGM/pk\_ratio.sas OUT=REPORT/OUTPUT/pk\_ratio\_ra\_k\_1\_2\_i.rtf (30SEP2013 - 16:59)

**Conclusions:** Bioequivalence and bio-equipotency could be demonstrated for HOE901-U300 (b) (4) (treatment T) and HOE901-U300 (b) (4) (treatment R).

Both HOE901-U300 formulations were well tolerated with no meaningful differences in safety-related parameters between treatments.

**Date of report:** 25-Feb-2014

## Single Dose PKPD in Japanese PKD12270:

Clinical Study Report  
HOE901-PKD12270

22-Oct-2013  
Version number: 2

### SYNOPSIS

|   |   |
|---|---|
| <b>Title of the study:</b> 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 PKD12270)  |   |
| <b>Investigator:</b> Dr. Masanari Shiramoto, Hakata Clinic, Clinical Pharmacology Center, Medical Co. LTA Clinical Pharmacology Research Clinic, Random square 5F-7F, 6-18, Tenyamachi, Hakata-ku, Fukuoka, 812-0025  |   |
| <b>Study center:</b> 1 site in Japan  |   |
| <b>Publications (reference):</b> Not applicable   |   |
| <b>Study period:</b>  |   |
| Date first patient enrolled:  | 11 November 2011  |
| Date last patient completed:  | 07 April 2012   |
| <b>Phase of development:</b> 1  |   |
| <b>Objectives:</b>  |   |
| <ul style="list-style-type: none"><li>• Primary objective:<ul style="list-style-type: none"><li>- To compare the metabolic effect of two different HOE901-U300 doses versus 0.4 U/kg Lantus®.</li></ul></li><li>• Secondary objectives:<ul style="list-style-type: none"><li>- To compare the pharmacokinetic profile of two different HOE901-U300 doses versus 0.4 U/kg Lantus®</li><li>- To compare the duration of action of different HOE901-U300 doses versus 0.4 U/kg Lantus®</li><li>- To explore the dose response relationship of HOE901-U300</li><li>- To explore the dose exposure relationship of HOE901-U300</li><li>- To assess the safety and tolerability of HOE901-U300.</li></ul></li></ul> |   |
| <b>Methodology:</b> 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  |   |
| <b>Number of patients:</b>  | Planned: 18 (to have 15 patients for pharmacodynamic evaluation)<br>Randomized: 18<br>Treated: 18 |
| <b>Evaluated:</b>   | Pharmacodynamics: 18<br>Safety: 18<br>Pharmacokinetics: 18  |
| <b>Diagnosis and criteria for inclusion:</b> 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<sub>1</sub>): Single dose injection of 0.4 U/kg HOE901-U300

Test 2 (T<sub>2</sub>): Single dose injection of 0.6 U/kg HOE901-U300

Batch numbers: 0F024A (Reference) and C1011129 (T<sub>1</sub> and T<sub>2</sub>)

#### 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].

Batch numbers: K0J94, K1G82 (Glucose), M1G82 (Sodium chloride), A484 (Heparin sodium) and 1E005A, 1K006A (Apidra®) (provided by site)

**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<sub>0-36</sub>)

Secondary:

- Time to 50% of GIR-AUC<sub>0-36</sub> (T<sub>50%</sub>-GIR-AUC<sub>0-36</sub>)
- Maximum smoothed body weight standardized GIR (GIR<sub>max</sub>)
- Time to GIR<sub>max</sub> (GIR-T<sub>max</sub>)
- Duration from dosing to the last value of smoothed blood glucose (BG) concentration versus time curve at or below 5.8 mmol/L (105 mg/dL) (Duration of euglycemia)
- Durations from dosing to the last value of smoothed BG concentration versus time curve at or below 6.1, 7.2 and 8.3 mmol/L (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-AUC<sub>0-36</sub>)
- Area under the insulin glargine concentration versus time curve from time zero to 24 hours post dosing (INS-AUC<sub>0-24</sub>)
- Time to 50% of INS-AUC<sub>0-36</sub> (T<sub>50%</sub>-INS-AUC<sub>0-36</sub>)
- Maximum insulin concentration (INS-C<sub>max</sub>)
- Time to C<sub>max</sub> (INS-T<sub>max</sub>)

**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<sub>1</sub> and T<sub>2</sub>) with the reference (R) treatments. For log transformed GIR-AUC<sub>0-36</sub> and GIR-AUC<sub>0-24</sub>, the ratios of test (T<sub>1</sub> and T<sub>2</sub>) 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-AUC<sub>0-36</sub> and GIR-AUC<sub>0-24</sub>. T<sub>50%</sub>-GIR-AUC<sub>0-36</sub> and "duration of euglycemia" were compared non-parametrically between test (T<sub>1</sub> and T<sub>2</sub>) and reference (R) treatments. GIR<sub>max</sub>, GIR-T<sub>max</sub> 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<sub>1</sub> and T<sub>2</sub>) against the reference treatment (R).

For log transformed INS-AUC<sub>0-36</sub>, the exposure of test (T<sub>1</sub> and T<sub>2</sub>) 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<sub>0-36</sub>. T<sub>50%</sub>-INS-AUC<sub>0-36</sub> 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:**

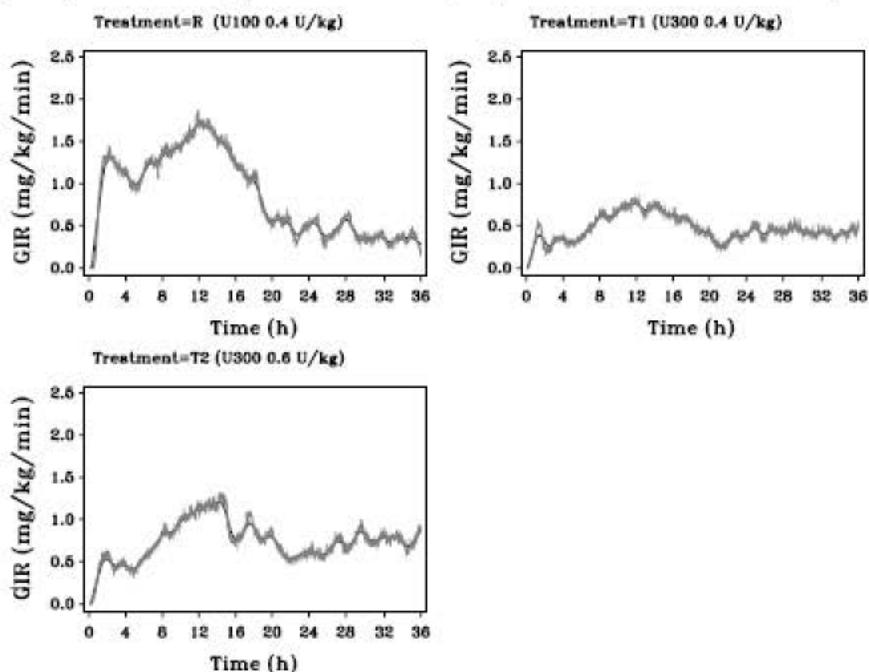
Mean and median smoothed glucose infusion rates (GIR) for the test treatments of HOE901-U300 (T<sub>1</sub> and T<sub>2</sub>) gradually increased until approximately T12H, and thereafter slightly declined, and then remained fairly stable from approximately T24H until the end of the clamp at T36H.

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<sub>0-36</sub>, increased with increasing HOE901-U300 dose, but was lower compared to R. Point estimates for GIR-AUC<sub>0-36</sub> ratios (90%CI) are: T<sub>1</sub>/R 0.11 (0.04 to 0.33) and T<sub>2</sub>/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<sub>max</sub>) was lower for the HOE901-U300 treatments, and the T<sub>50%</sub>-GIR-AUC<sub>0-36</sub> median values were somewhat longer.

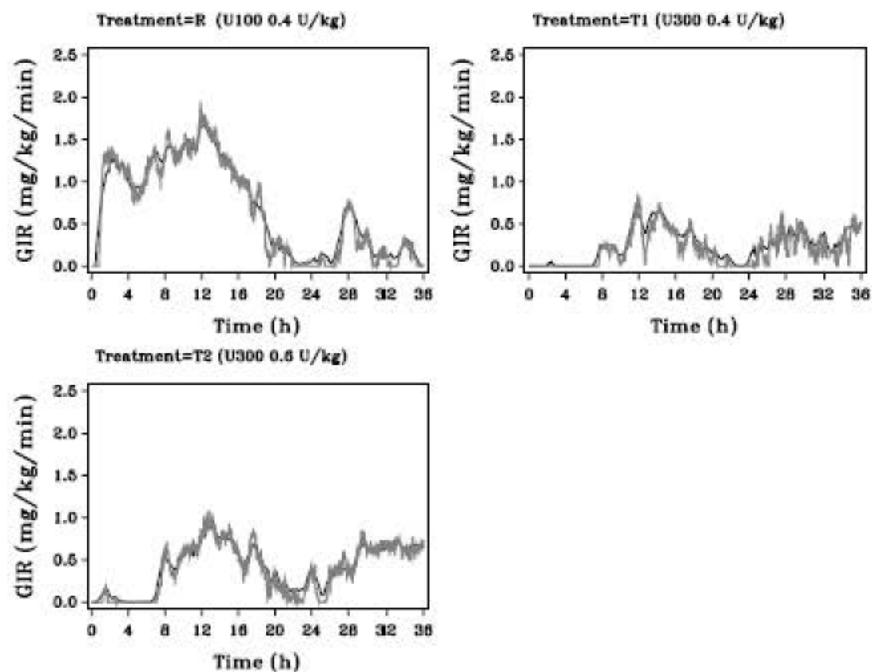
**Body Weight standardized glucose infusion rate (GIR) – Mean raw and mean smoothed profiles**



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\_girmeanal\_d\_g.sas OUT=REPORT/OUTPUT/pd\_girmeanal\_d\_g.j.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).

PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/pd\_girmedianall\_d\_g.sas OUT=REPORT/OUTPUT/pd\_girmedianall\_d\_g\_i.rf (29MAY2012 - 18:50)

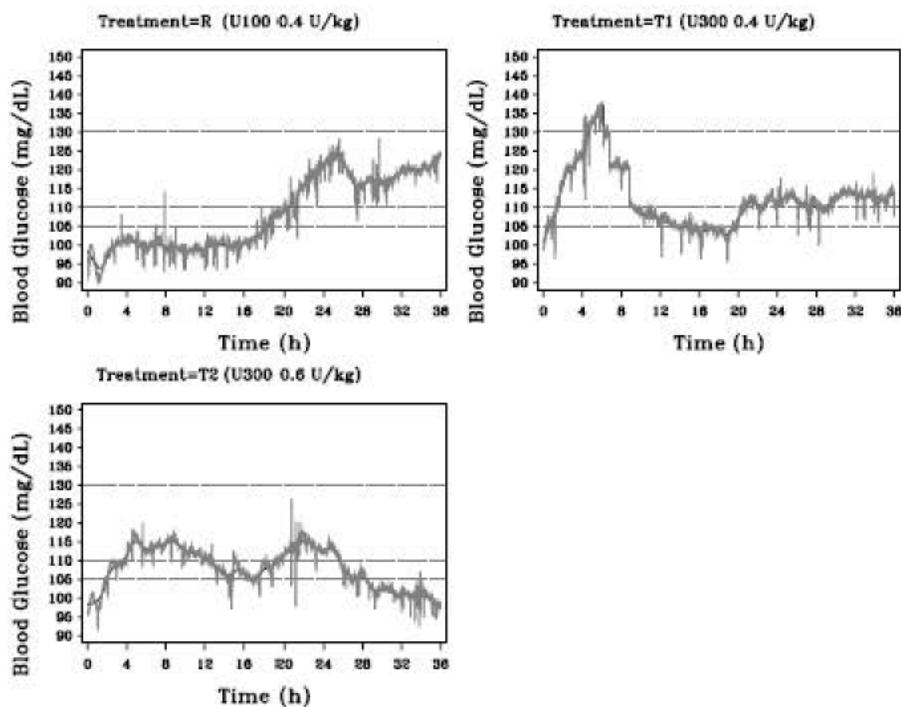
| PD parameters of body weight standardized glucose infusion rate (GIR)  |                   |                    |                    |
|--|-------------------|--------------------|--------------------|
|  | R (U100 0.4 U/kg) | Test treatment     |                    |
|  |                   | T1 (U300 0.4 U/kg) | T2 (U300 0.6 U/kg) |
| <b>GIR-AUC(0-24h) (mg/kg)</b>  |                   |                    |                    |
| 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       |
| <b>GIR-AUC(0-36h) (mg/kg)</b>  |                   |                    |                    |
| 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      |
| <b>GIR-AUC(12-36h) (mg/kg)</b>   |                   |                    |                    |
| 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      |
| <p>GIR = body weight standardized glucose infusion rate<br/>                     GIR-AUC values of zero were replaced by 1 mg/kg.<br/>                     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).<br/>                     PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/pd_desogauc_d_t.sas OUT=REPORT/OUTPUT/pd_desogauc_d_t.rtf (29MAY2012 - 18:54)</p> |                   |                    |                    |

| 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)     |
| <p>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).</p> <p>GIRmax is based on smoothed GIR profiles.</p> <p>PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/pd_pkd12270.sas OUT=REPORT/OUTPUT/pd_gir_ba_k_t_2_i.rtf (29MAY2012 - 18:58)</p>   |                   |                    |                    |
| <b>Maximum smoothed body weight standardized glucose infusion rate [GIRmax] - descriptive statistics</b>  |                   |                    |                    |
|   |                   | Test treatment     |                    |
|   | R (U100 0.4 U/kg) | T1 (U300 0.4 U/kg) | T2 (U300 0.6 U/kg) |
| <b>GIRmax (mg/kg/min)</b>   |                   |                    |                    |
| 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          |
| <p>GIR = body weight standardized glucose infusion rate<br/>GIRmax values of zero were replaced by 0.001 mg/kg/min.<br/>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).<br/>PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/pd_descgmax_d_t_i.sas OUT=REPORT/OUTPUT/pd_descgmax_d_t_i.rtf (29MAY2012 - 18:33)</p>  |                   |                    |                    |
| <b>PD parameter T50%-GIR-AUC0-36</b>  |                   |                    |                    |
|   |                   | Test treatment     |                    |
|   | R (U100 0.4 U/kg) | T1 (U300 0.4 U/kg) | T2 (U300 0.6 U/kg) |
| <b>T50% GIR-AUC(0-36) (h)</b>   |                   |                    |                    |
| 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        |
| <p>GIR = body weight standardized glucose infusion rate<br/>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).<br/>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).<br/>PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/pd_descgauct50_d_t_i.sas OUT=REPORT/OUTPUT/pd_descgauct50_d_t_i.rtf (29MAY2012 - 18:33)</p> |                   |                    |                    |

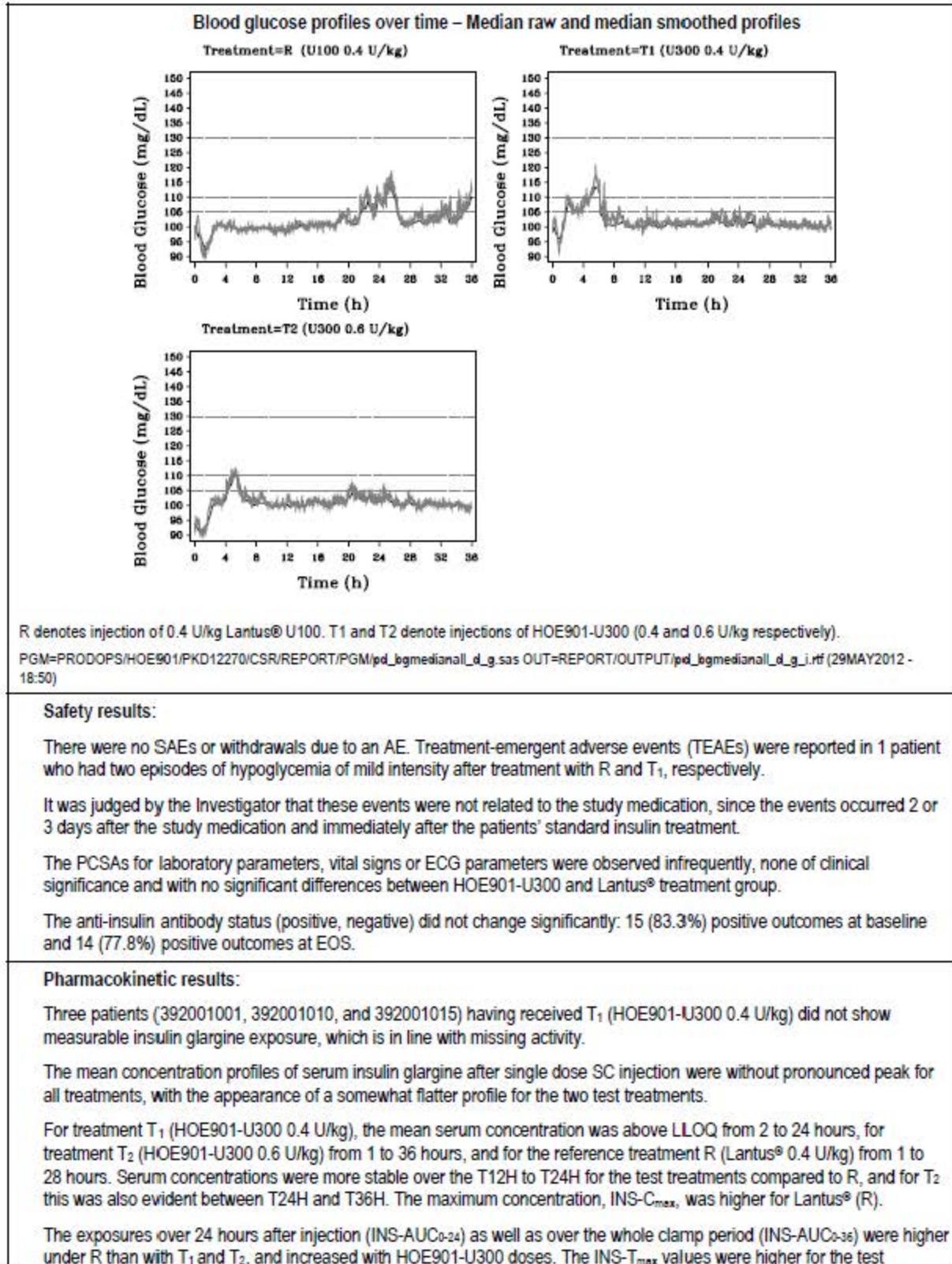
The shape of mean smoothed blood glucose (BG) profiles exhibited somewhat similar characteristics for the two test treatments, T<sub>1</sub> and T<sub>2</sub>. Blood glucose increased up to about T6H, reflecting the time needed for T<sub>1</sub> and T<sub>2</sub> to take effect, with a larger increase observed following the low dose test treatment T<sub>1</sub>. For both T<sub>1</sub> and T<sub>2</sub>, blood glucose subsequently stabilized below the predefined glucose control threshold of 6.7 mmol/L (120 mg/dL) throughout the duration of the clamp (36 hours). In contrast, for the treatment R, mean smoothed BG values were maintained below 6.7 mmol/L (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<sub>1</sub> and T<sub>2</sub> during the initial hours, but higher for R than for T<sub>1</sub> and T<sub>2</sub> beyond T16H, consistent with the slower onset but more sustained action of the test treatments T<sub>1</sub> and T<sub>2</sub>.

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



R denotes injection of 0.4 U/kg Lantus® U100. T<sub>1</sub> and T<sub>2</sub> denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).  
PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/jpd\_logmeanall\_d\_g.sas OUT=REPORT/OUTPUT/jpd\_logmeanall\_d\_g\_i.rtf (29MAY2012 - 18:54)

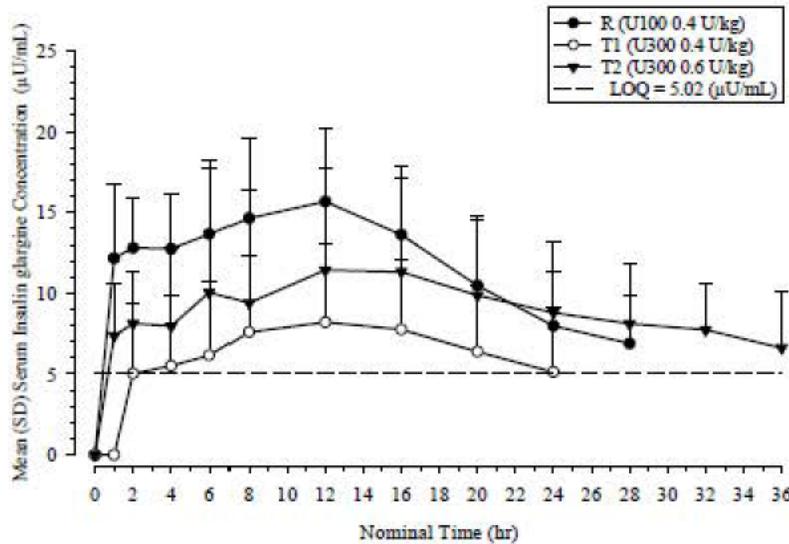


treatments T<sub>1</sub> and T<sub>2</sub>.

The point estimates of the treatment ratios for INS-AUC<sub>0-36</sub> (90%CI) were: T<sub>1</sub>/R 0.62 (0.51; 0.75) and T<sub>2</sub>/R 0.75 (0.59; 0.94).

The apparently somewhat flatter profiles of T<sub>1</sub> and T<sub>2</sub> compared to R are also reflected in the times to reach 50% of the exposure over the whole clamp period (T<sub>50%-INS-AUC<sub>0-36</sub></sub>); the medians were about 17 and 18 hours for T<sub>1</sub> and T<sub>2</sub>, 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<br>(Geometric Mean) [CV%]           | Serum Insulin glargine       |                              |                              |
|---|------------------------------|------------------------------|------------------------------|
|   | R (U100 0.4 U/kg)            | T1 (U300 0.4 U/kg)           | T2 (U300 0.6 U/kg)           |
| <b>N</b>                                      | 18                           | 15 <sup>b</sup>              | 18                           |
| <b>INS-C<sub>max</sub></b><br>(µU/mL)         | 17.3 ± 4.75<br>(16.6) [27.5] | 10.9 ± 3.39<br>(10.4) [31.2] | 13.8 ± 7.08<br>(12.3) [51.5] |
| <b>INS-T<sub>max</sub><sup>a</sup></b><br>(h) | 8.00<br>(1.00 - 16.00)       | 16.00<br>(1.00 - 32.00)      | 14.00<br>(1.00 - 32.00)      |
| <b>INS-AUC<sub>0-24</sub></b><br>(µU·h/mL)    | 303 ± 78.8<br>(291) [26.0]   | 190 ± 66.5<br>(176) [35.0]   | 232 ± 123<br>(NA) [52.9]     |
| <b>INS-AUC<sub>0-36</sub></b><br>(µU·h/mL)    | 370 ± 101<br>(352) [27.2]    | 251 ± 91.6<br>(233) [36.4]   | 326 ± 156<br>(262) [47.8]    |

<sup>a</sup> Median (Min - Max) NA (not applicable)

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

<sup>b</sup> 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 <sub>max</sub>   | 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.<br>T1 and T2 (test treatments) denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).<br>LOQ values were set to zero for PK analysis.<br>PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/PK_PKD12270.sas OUT=REPORT/OUTPUT/pk_ins_ka_k_t_2_i.rf (22MAY2012 - 10:49)   |                   |                    |                    |
| PK parameter T <sub>50%-INS-AUC</sub> <sub>0-36</sub>  |                   |                    |                    |
|  | R (U100 0.4 U/kg) | Test treatment     |                    |
|  |                   | T1 (U300 0.4 U/kg) | T2 (U300 0.6 U/kg) |
| T <sub>50%-INS-AUC</sub> (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<br>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).<br>R (reference treatment) denotes injection of 0.4 U/kg Lantus®U100.<br>T1 and T2 (test treatments) denote injections of HOE901-U300 (0.4 and 0.6 U/kg respectively).<br>PGM=PRODOPS/HOE901/PKD12270/CSR/REPORT/PGM/pkd_insudesc_kd_t.sas OUT=REPORT/OUTPUT/pkd_insudesc_kd_t_2_i.rf (03JUL2012 - 13:39)          |                   |                    |                    |
| <b>Conclusions:</b>  |                   |                    |                    |
| <b>Pharmacodynamics:</b>   |                   |                    |                    |
| GIR and BG profiles for T <sub>1</sub> and T <sub>2</sub> were different from R (Lantus®). GIR for R continuously increased until T12H and then declined until clamp end, which is consistent with the observation of BG values maintained at the euglycemic level early during the clamp which then increased towards clamp end. In contrast, HOE901-U300 treatments showed a later and smaller maximum GIR and generally sustained pharmacodynamic effects for the 36 hours of the clamp, more evident with T <sub>2</sub> than T <sub>1</sub> . |                   |                    |                    |
| Due to the predefined clamp end at T36H, the full duration of HOE901-U300 activity could not be assessed, and there could be glucose lowering activity beyond 36 hours post dose.  |                   |                    |                    |
| Treatment with T <sub>1</sub> and T <sub>2</sub> required an overall lower amount of exogenously administered glucose (expressed as GIR-AUC <sub>0-36</sub> ) compared to R.   |                   |                    |                    |
| The euglycemic BG levels observed with R were achieved at the expense of a greater GIR and hence greater GIR-AUC. In contrast, T <sub>1</sub> and T <sub>2</sub> , after an initial period of sub-optimally controlled BG levels, maintained BG levels within predefined euglycemic clamp limit at a low GIR.  |                   |                    |                    |

**Safety:**

All treatments were well tolerated with no differences in safety related parameters between treatments.

**Pharmacokinetics:**

After single dose subcutaneous injection, the mean serum concentration profiles of HOE901-U300 treatments were different from those of Lantus® in that they were somewhat flatter over the observation periods. The concentrations for T<sub>1</sub> and T<sub>2</sub> increased with dose. Reference treatment (R) displayed a higher serum concentration of insulin glargine during the anterior half of the clamp period and a more rapid decline after 12 hours than T<sub>1</sub> and T<sub>2</sub>.

In conclusion, PK and PD results show the HOE901-U300 formulation to have an even flatter exposure and activity profiles than Lantus® after single dose administration, providing for sustained duration of action beyond 24 hours with somewhat slower onset of action.

Date of report: 22-Oct-2013

## Study PDY12335

Clinical Study Report  
HOE901-PDY12335 - Insulin glargine

20-Nov-2013  
Version number: 1

## SYNOPSIS

|   |  |
|---|--|
| <b>Title of the study:</b> A randomized, open-label, 2-treatment crossover study of a new formulation of insulin glargine comparing to Lantus® on 24-hour glucose profile in Japanese patients with type 1 diabetes mellitus on treatment with basal-bolus insulin (PDY12335)   |  |
| <b>Investigator:</b>  | Dr Hideaki Jinnouchi, Jinnouchi-Hospital, 6-2-3, Kuhonji, Chuo-ku, Kumamoto City, Kumamoto Prefecture, 826-0976, Japan |
| <b>Study center:</b>  | 1 center in Japan  |
| <b>Publications (reference):</b> Not applicable   |  |
| <b>Study period:</b>  |  |
| Date first patient enrolled:  | 12 September 2012  |
| Date last patient completed:  | 08 August 2013   |
| <b>Phase of development:</b> Phase 1  |  |
| <b>Objectives:</b>  |  |
| <b>Primary:</b> To compare the 24-hour glycemic profile in continuous glucose monitoring (CGM) between a new formulation of insulin glargine (HOE901-U300) and Lantus at steady state   |  |
| <b>Secondary:</b>   |  |
| <ul style="list-style-type: none"><li>• To compare the change of fasting plasma glucose (FPG), self monitoring of plasma glucose (SMPG), and postprandial plasma glucose (PPG) between the 2 treatments</li><li>• To compare the efficacy of the 2 treatments on glycemic control in glycemic parameters (1,5-anhydroglucitol [1,5 AG], glycoalbumin, and hemoglobin A1c [HbA1c])</li><li>• To compare the occurrence of hypoglycemia between the 2 treatments</li><li>• To assess the safety and tolerability of HOE901-U300</li></ul> |  |
| <b>Methodology:</b> Single-center, randomized, open-label, active control, repeated dose, crossover (2-sequence, 2-period, and 2-treatment with no washout period between treatment periods) study  |  |
| <b>Number of patients:</b>  | Planned: 20<br>Randomized: 20<br>Treated: 20   |
| <b>Evaluated:</b>   | Efficacy: 20<br>Safety: 20<br>Pharmacokinetics: 20   |
| <b>Diagnosis and criteria for inclusion:</b> Japanese patients aged over 20 years with type 1 diabetes mellitus (T1DM) on treatment with basal-bolus insulin  |  |

**Study treatments:**

**Investigational medicinal products (IMPs):** HOE901-U300 (Test) and Lantus (Comparative)

**Formulations:**

HOE901-U300: Solution containing insulin glargine (300 U/mL)

Lantus: Solution containing insulin glargine (100 U/mL)

**Route of administration:** Subcutaneous (SC) injection

**Dose regimen:** The dose of HOE901-U300 or Lantus was individually up-titrated. If previous basal insulin was administered twice daily (BID) or once daily (QD) in the morning, the basal insulin regimen was changed to QD at bedtime at Visit 1 (screening). If Lantus was administered BID, the previous total daily dose was given QD. If previous basal insulin other than Lantus was administered BID, then 80% of the previous total daily dose was given QD.

HOE901-U300

The starting dose of HOE901-U300 (Treatment Period 1 or Treatment Period 2) was at a dose divisible by 1.5 and did not exceed the previous QD basal insulin dose. After administration of the starting dose, the dose of HOE901-U300 was adjusted individually to achieve a target glycemic goal of 80 to 130 mg/dL in FPG measured by SMPG according to the titration schedule.

Lantus

The starting dose of Lantus (Treatment Period 1 or Treatment Period 2) was the same as the previous QD basal insulin dose. After administration of the starting dose, the dose of Lantus was adjusted individually to achieve the target glycemic goal of 80 to 130 mg/dL in FPG measured by SMPG according to the titration schedule.

The timing of administration of HOE901-U300 and Lantus was at the same time throughout the entire study period (bedtime), and it was preferable to administer HOE901-U300 or Lantus at 3 hours or more after administration of the evening meal bolus insulin.

**Batch numbers:** HOE901-U300: C1011129; Lantus: C1024081

**Noninvestigational medicinal product:** Marketed mealtime insulin such as insulin lispro, aspart, and glulisine

**Route of administration:** Subcutaneous injection

**Duration of treatment:** 57 days

**Duration of observation:** Approximately 66 days including screening (7 days [+7 days, -3 days]), Treatment Period 1 (28 days  $\pm$ 3 days), Treatment Period 2 (29 days  $\pm$ 3 days), and Follow-up (2 days  $\pm$ 1 day).

**Criteria for evaluation:**

**Efficacy:**

Primary: Absolute area under the concentration time curve (AUC) above and below the individual average plasma glucose value (AGV) on the 2nd day of CGM ( $AUC_{mean\_24h}$ ).

(Note): 1st day: 0-24 hours data from 3 days of CGM (Day -3 to Day -2, Day 26 to Day 27, and Day 54 to Day 55)  
2nd day: 24-48 hours data from 3 days of CGM (Day -2 to Day -1, Day 27 to Day 28, and Day 55 to Day 56)  
3rd day: 48-72 hours data from 3 days of CGM (Day -1 to Day 1, Day 28 to Day 29, and Day 56 to Day 57)  
(1st day and 2nd day were conducted in hospital)

**Secondary:**

- Absolute AUC above and below the individual AGV on the 2nd day of CGM at nocturnal time ( $AUC_{mean\_noc}$ ) and at daytime ( $AUC_{mean\_daytime}$ )
  - Nocturnal time, 0:00 to 06:00; Daytime, 06:00 to 24:00.
- Absolute AUC above and below the defined blood glucose value (80, 100, 120, and 140 mg/dL) on the 2nd day of CGM ( $AUC_{value\_24h}$ ), at nocturnal time ( $AUC_{value\_noc}$ ), and at daytime ( $AUC_{value\_daytime}$ )
- J-Index
- M value
- Hyperglycemic index, hypoglycemic index and Index of Glycemic Control (ICG)
- Mean Amplitude of Glycemic Excursions (MAGE)
- Mean of Daily Difference (MODD)
- Parameters from target blood glucose (TBG) range (80 to 140 mg/dL)
  - Duration of TBG range over 24 hours ( $Dur_{TBG[80-140]}$ )
  - Rate of TBG range over 24 hours ( $Rate_{TBG[80-140]}$ )
  - AUC above (140 mg/dL) and below (80 mg/dL) plasma glucose value on the 2nd day of CGM ( $AUC_{over140}$ ,  $AUC_{under80}$ , respectively)
- Range [min-max] of glucose value during 3 hours just before bedtime injection ( $BG_{Just\ before\ inj}$ )
- Maximum duration within fixed blood glucose value range ( $Dur_{within30mg/dL}$ ,  $Dur_{within60mg/dL}$ ,  $Dur_{within90mg/dL}$ , and  $Dur_{within120mg/dL}$ )
  - Duration of fixed blood glucose range (30, 60, 90, and 120 mg)
  - Duration of fixed blood glucose range (30, 60, 90, and 120 mg) in nocturnal term
- Minimum blood glucose range of fixed hour (16, 18, 20, and 22 hours) residence time
  - ( $MIR_{16hRT}$ ,  $MIR_{18hRT}$ ,  $MIR_{20hRT}$ ,  $MIR_{22hRT}$ , and  $MIR_{24hRT}$ )
- Change in FPG, SMPG, and PPG from overall baseline to each treatment end, by treatment
- Change in glycemic parameters (1,5 AG, glycoalbumin, and HbA1c) from overall baseline to each treatment end, by treatment
- Change in daily insulin dose from overall baseline to each treatment end, by treatment (absolute and per kg body weight):
  - Change in daily basal insulin dose
  - Change in daily mealtime insulin dose
  - Change in daily total insulin dose

**Safety:** Patients were monitored for safety via adverse events (AEs) spontaneously reported by the patients or observed by the Investigator, injection site and hypersensitivity reactions, clinical laboratory data, vital signs, electrocardiogram (ECG), hypoglycemia, and immunogenicity (presence of anti-insulin antibodies).

**Pharmacokinetics:** The concentration observed just before treatment administration during repeated dosing ( $C_{trough}$ ) of insulin glargine at steady state for both treatments was measured.

**Pharmacokinetic sampling times and bioanalytical methods:**

Blood samples for the analysis of serum insulin glargine were collected at Day -3 or Day -2 (baseline), Day 26 or Day 27, and Day 54 or Day 55. Blood samples were taken just before the injection of bedtime insulin (marketed basal insulin or IMPs).

Concentrations of serum insulin glargine were analyzed using a radioimmunoassay nonspecific for insulin with a lower limit quantification of 5.02  $\mu$ U/mL.

**Statistical methods:**

**Efficacy:** The difference in variability between HOE901-U300 and Lantus on 24-hour CGM was examined by exploratory analysis using  $AUC_{mean,24h}$ . Using glucose data from only the 2nd day of CGM, the log transformed  $AUC_{mean,24h}$  ratio between the 2 formulations with 90% confidence intervals (CIs) was analyzed with a linear mixed effect model with fixed terms for sequence, period, and formulation, and with an unstructured 2 by 2 matrix of formulation-specific variances and covariances for subject within sequence blocks.

For nocturnal analysis, the variability in blood glucose was evaluated using the same analysis approach as for 24-hour CGM.

The changes in FPG, SMPG, PPG, 1,5 AG, glycoalbumin, and HbA1c from overall baseline to each treatment end were analyzed.

**Safety:** The evaluation of IMP and active comparator was based on the review of individual numbers and values of hypoglycemic events, anti-insulin antibodies, major adverse cardiac events (MACE), AEs, vital signs, ECGs, hematology and biochemistry [out of normal range and potentially clinically significant abnormalities (PCsAs)] and descriptive statistics. Treatment-emergent adverse events (TEAEs) were tabulated (counts and percents) by formulation. End-of-study PCsAs in clinical laboratory test results, vital signs, and ECGs were listed.

**Pharmacokinetics:** Descriptive statistics for  $C_{trough}$  for each period were provided by treatment and  $C_{trough}$  values were listed by treatment, patient, and period.

**Summary:**

**Population characteristics:**

A total of 20 patients with T1DM were randomized to 1 of 2 treatment sequences: Lantus in Treatment Period 1 followed by HOE901-U300 in Treatment Period 2 (n = 10), HOE901-U300 in Treatment Period 1 followed by Lantus in Treatment Period 2 (n = 10). All 20 patients completed the study.

Demographic and baseline characteristics were balanced between treatment sequences except for mean daily insulin doses. The patients that received HOE901-U300 first (n=10) had higher mean basal and mealtime insulin doses at baseline than the patients who received Lantus in the first treatment period (n = 10). The mean age of the study population was 52.1 years. All patients were Asian/Oriental. The mean body mass index at baseline was 23.36 kg/m<sup>2</sup>. The mean HbA1c at baseline was 8.21% and the mean FPG at baseline was 7.79 mmol/L (140.3 mg/dL).

#### Efficacy results:

##### *Primary efficacy endpoint:*

The mean (standard deviation;[SD])  $AUC_{mean\_24h}$  (2nd day of CGM) value was slightly lower for HOE901-U300 compared to Lantus (59756.55 [24577.90] min\*mg/dL and 60409.12 [19925.75] min\*mg/dL, respectively). The point estimate of the treatment ratio was 0.959 [90% CI: 0.794 to 1.158].

Graphical presentation of mean CGM profiles from Day 2 18:00 to Day 3 24:00 of CGM periods (Figure 1) suggested similar glucose variability over time between the HOE901-U300 and the Lantus treatments.

##### *Secondary efficacy endpoints:*

The  $AUC_{mean\_noc}$  value (0:00 to 06:00 of the 2nd day of CGM) for HOE901-U300 was slightly lower compared to Lantus. Mean (SD) of  $AUC_{mean\_noc}$  was 5337.21 (3467.41) min\*mg/dL for HOE901-U300 and 5551.80 (4304.49) min\*mg/dL for Lantus. The point estimate of the treatment ratio was 0.939 [90% CI: 0.693 to 1.273].

The duration of TBG over 24 hours was comparable for each treatment. The mean (SD) of  $Dur_{TBG(80-140)}$  was 8.71 (5.92) hours for the HOE901-U300 group and 8.63 (5.18) hours for the Lantus group. Point estimate of treatment ratio was 0.958 [90% CI: 0.330 to 2.781].

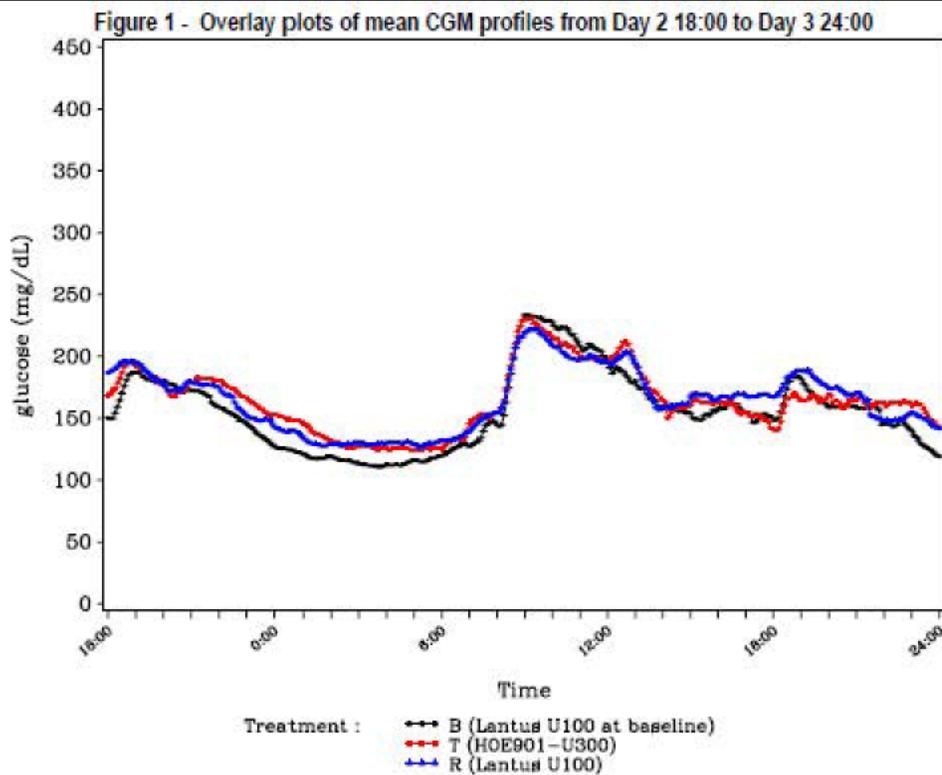
To eliminate the influences of glycemic excursions by meals and snacks,  $MIR_{16hRT}$ ,  $MIR_{18hRT}$ ,  $MIR_{20hRT}$ ,  $MIR_{22hRT}$  and  $MIR_{24hRT}$  were evaluated and were comparable between the 2 treatments. The means (SD) of  $MIR_{16hRT}$ ,  $MIR_{18hRT}$ ,  $MIR_{20hRT}$ ,  $MIR_{22hRT}$ , and  $MIR_{24hRT}$  were 81.21 (31.83) mg/dL, 103.42 (39.61) mg/dL, 127.63 (49.21) mg/dL, 157.37 (57.86) mg/dL, and 200.79 (62.65) mg/dL in the HOE901-U300 group and 84.65 (33.82) mg/dL, 105.60 (39.13) mg/dL, 129.00 (45.09) mg/dL, 152.25 (49.05) mg/dL, and 198.20 (59.31) mg/dL in the Lantus group respectively.

Glycemic control appeared to be comparable between the 2 treatments with similar mean changes from baseline observed in 1,5 AG, glycoalbumin, and HbA1c.

For 1,5 AG, the changes from baseline ranged from -1.16 to 4.26  $\mu\text{mol/L}$  (-0.19 to 0.70  $\mu\text{g/mL}$ ) for patients given Lantus followed by HOE901-U300 and from 3.35 to 6.15  $\mu\text{mol/L}$  (0.55 to 1.01  $\mu\text{g/mL}$ ) for patients given HOE901 U300 followed by Lantus.

For glycoalbumin, the changes from baseline ranged from -1.15% to 0.28% for patients given Lantus followed by HOE901-U300 and from -1.31% to -0.39% for patients given HOE901-U300 followed by Lantus.

For HbA1c, the changes from baseline in each period were -0.27% and -0.13% for patients given Lantus followed by HOE901-U300 and were -0.28% and -0.25% for patients given HOE901-U300 followed by Lantus.



CGM=continuous glucose monitoring

This figure is plotted using mean value by 5 min.

PGM=PRODOPS/HOE901/PDY12335/CSR/REPORT/PGM/pd\_cgmmover\_m\_g.sas

OUT=REPORT/OUTPUT/pd\_cgmmover\_m\_g\_i.rtf(18SEP2013 - 18:23)

Basal insulin doses generally increased from the overall baseline for both treatment sequences (at baseline of Period 1/overall baseline, the mean daily basal insulin dose was 14.85 units in the HOE901-U300 group and 11.70 units in the Lantus group; at endpoint of Period 1, HOE901-U300: 18.13 units; Lantus: 13.14 units; at baseline of Period 2, HOE901-U300: 12.75 units; Lantus: 18.40 units; at endpoint of Period 2, HOE901-U300: 14.53 units; Lantus: 18.10 units).

Mean mealtime insulin daily doses were generally stable within both sequence arms throughout the study (at baseline of Period 1, HOE901-U300: 30.60 units; Lantus: 24.90 units; at endpoint of Period 1, HOE901-U300: 29.90 units; Lantus: 24.50 units; at baseline of Period 2, HOE901-U300: 25.40 units; Lantus: 29.80 units; at endpoint of Period 2, HOE901-U300: 25.24 units; Lantus: 29.59 units).

Mean basal and mealtime insulin doses (total insulin) at baseline for patients given HOE901-U300 in Period 1 followed by Lantus in Period 2 were higher than those of patients given Lantus in Period 1 followed by HOE901-U300 in Period 2.

**Safety results:**

There were no treatment-emergent serious adverse events (SAEs), deaths, or any withdrawals due to an AE in this study. The percentage of patients with any TEAE was higher for HOE901-U300 (9/20 [45.0 %]) than for the Lantus treatment (4/20 [20.0 %]). However, no TEAEs were classified as related to the IMP. No TEAEs linked to injection site reactions were observed for either treatment. While an accidental overdose of mealtime insulin (Apidra) was reported, no hypoglycemia were associated with this event.

The most frequently reported TEAE was nasopharyngitis (other than hypoglycemic events), with 4 TEAEs reported by 4 patients. Of the 4 TEAEs, 2 were reported following HOE901-U300 and 2 were reported following Lantus. In addition, there were a number of TEAEs classified as gastrointestinal disorders reported by patients during the treatment period in which they received HOE901-U300; 1/20 patients reported a TEAE of abdominal discomfort, 1/20 patients reported a TEAE of dental caries, 1/20 patients reported TEAE of stomatitis, and 1/20 patients reported a TEAE of vomiting. All other TEAEs were reported by 1 patient only.

During the on-treatment period, 17/20 patients (85.0%) experienced at least 1 hypoglycemic event for the HOE901-U300 treatment and 20/20 patients (100%) for the Lantus treatment (Table 1). In addition, the total number of reported hypoglycemic events was slightly lower for the HOE901-U300 treatment than the Lantus treatment, with 126 and 192 events reported, respectively (Table 2). Of these hypoglycemic events, 6 were reported as nocturnal (00:00 to 05:59) during HOE901-U300 treatment with 20 nocturnal events reported during Lantus treatment.

There were a low number of PCSAs reported during the study for laboratory parameters, vital signs, and ECG parameters, but none were considered to be clinically significant and there were no relevant differences between HOE901-U300 and Lantus treatments.

**Table 1 - Number (%) of patients with at least one hypoglycemia event during the on-treatment period - safety population**

| Type of hypoglycemia event<br>n(%)                | All hypoglycemia      |                  | Nocturnal hypoglycemia<br>(00:00-05:59) |                  |
|---|-----------------------|------------------|---|------------------|
|   | HOE901-U300<br>(N=20) | Lantus<br>(N=20) | HOE901-U300<br>(N=20)                   | Lantus<br>(N=20) |
| Any hypoglycemia event                            | 17 (85.0%)            | 20 (100%)        | 4 (20.0%)                               | 8 (40.0%)        |
| Documented symptomatic hypoglycemia               |                       |                  |   |                  |
| ≤3.9 mmol/L (70 mg/dL)                            | 14 (70.0%)            | 18 (90.0%)       | 3 (15.0%)                               | 7 (35.0%)        |
| < 3.0 mmol/L (54 mg/dL)                           | 8 (40.0%)             | 12 (60.0%)       | 1 (5.0%)                                | 4 (20.0%)        |
| Asymptomatic hypoglycemia                         |                       |                  |   |                  |
| ≤3.9 mmol/L (70 mg/dL)                            | 10 (50.0%)            | 13 (65.0%)       | 2 (10.0%)                               | 2 (10.0%)        |
| < 3.0 mmol/L (54 mg/dL)                           | 2 (10.0%)             | 3 (15.0%)        | 0                                       | 0                |
| Relative hypoglycemia                             |                       |                  |   |                  |
| > 3.9 mmol/L (70 mg/dL)                           | 0                     | 1 (5.0%)         | 0                                       | 0                |
| Severe and/or confirmed <sup>a</sup> hypoglycemia |                       |                  |   |                  |
| ≤3.9 mmol/L (70 mg/dL)                            | 17 (85.0%)            | 20 (100%)        | 4 (20.0%)                               | 8 (40.0%)        |
| < 3.0 mmol/L (54 mg/dL)                           | 8 (40.0%)             | 12 (60.0%)       | 1 (5.0%)                                | 4 (20.0%)        |

MedDRA16.0

<sup>a</sup>: Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL))

PGM=PRODOPS/HOE901/PDY12335/CSR/REPORT/PGM/ae\_hypo\_s\_t.sas OUT=REPORT/OUTPUT/ae\_hypo\_s\_t\_i.rtf(18SEP2013 - 18:02)

**Table 2 - Number of events with at least one hypoglycemia event during the on-treatment period - safety population**

| Type of hypoglycemia event                        | All hypoglycemia      |                  | Nocturnal hypoglycemia<br>(00:00-05:59) |                  |
|---|-----------------------|------------------|---|------------------|
|   | HOE901-U300<br>(N=20) | Lantus<br>(N=20) | HOE901-U300<br>(N=20)                   | Lantus<br>(N=20) |
| Any hypoglycemia event                            | 126                   | 192              | 6                                       | 20               |
| Documented symptomatic hypoglycemia               |                       |                  |   |                  |
| ≤3.9 mmol/L (70 mg/dL)                            | 75                    | 142              | 3                                       | 18               |
| <3.0 mmol/L (54 mg/dL)                            | 24                    | 40               | 1                                       | 6                |
| Asymptomatic hypoglycemia                         |                       |                  |   |                  |
| ≤3.9 mmol/L (70 mg/dL)                            | 51                    | 47               | 3                                       | 2                |
| <3.0 mmol/L (54 mg/dL)                            | 4                     | 4                | 0                                       | 0                |
| Relative hypoglycemia                             |                       |                  |   |                  |
| >3.9 mmol/L (70 mg/dL)                            | 0                     | 3                | 0                                       | 0                |
| Severe and/or confirmed <sup>a</sup> hypoglycemia |                       |                  |   |                  |
| ≤3.9 mmol/L (70 mg/dL)                            | 126                   | 189              | 6                                       | 20               |
| <3.0 mmol/L (54 mg/dL)                            | 28                    | 44               | 1                                       | 6                |

<sup>a</sup>: Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL))

PGM=PRODOPS/HOE901/PDY12335/CSR/REPORT/PGM/ae\_hypo\_e\_s\_t.sas OUT=REPORT/OUTPUT/ae\_hypo\_e\_s\_t.i.rtf (18SEP2013 - 19:29)

**Pharmacokinetic results:**

The mean (± SD) trough serum insulin concentrations for the 2 treatments was 33.1 ± 21.7 µU/mL for HOE901-U300 and 31.7 ± 27.0 µU/mL for Lantus, which did not differ greatly from the baseline value of 32.6 ± 16.8 µU/mL.

**Conclusions:**

Overall, the mean profiles on the 2nd day of CGM suggested similar glucose variability over time between the HOE901-U300 and the Lantus treatments. On the 2nd day of CGM,  $AUC_{mean\_24h}$  and  $AUC_{mean\_noc}$  were slightly lower for the HOE901-U300 treatment than for the Lantus treatment, however the treatment ratios of 0.959 and 0.939 did not indicate any significance.

In general, all other CGM parameters, FPG, SMPG, and PPG were comparable for the 2 treatments. Glycemic control was also comparable between the 2 treatments with similar mean changes from baseline observed in 1,5 AG, glycoalbumin, and HbA1c for both treatments.

HOE901-U300 and Lantus, administered in the evening, were well tolerated during the study period, and no specific safety concerns were observed. The overall percentage of patients with at least 1 hypoglycemic event and the number of events of hypoglycemia were lower for the HOE901-U300 treatment than for the Lantus treatment. This difference was even more pronounced when comparing only the nocturnal events. However, the numerical trends in favor of HOE901-U300 for hypoglycemia have to be interpreted with caution due to the small number of patients.

The number of TEAEs other than hypoglycemic events was low. The percentage of patients reporting a TEAE was higher for HOE901-U300 (9/20 [45.0 %]) than for Lantus treatment (4/20 [20.0 %]), however, no TEAEs were classified as related to the IMP.

At steady state the mean trough serum concentration of insulin glargine did not differ greatly between the 2 treatments, and were similar to the baseline value at the beginning of the study.

Date of report: 20-Nov-2013

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SZE W LAU  
01/28/2015

MANOJ KHURANA  
01/28/2015

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 206-538

**NDA Number: 206-538 Serial Applicant: Sanofi  
0000**

**Stamp Date: April 25, 2014**

**Drug Name: Insulin Glargine NDA Type: Original New Drug  
Application**

On **initial** overview of the NDA application for RTF:

|   | Content Parameter  | Yes | No | Comment  |
|---|--|-----|----|--|
| <b>Criteria for Refusal to File (RTF)</b>       |  |     |    |  |
| 1   | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?   | X   |    |  |
| 2   | Has the applicant provided metabolism and drug-drug interaction information?   |     | X  | This submission concerns the 3 times concentrated insulin glargine. Insulin glargine is an approved product. |
| <b>Criteria for Assessing Quality of an NDA</b> |  |     |    |  |
| <b>Data</b>                                     |  |     |    |  |
| 3   | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?   |     |    | Not applicable   |
| 4   | If applicable, are the pharmacogenomic data sets submitted in the appropriate format?  |     |    | Not applicable   |
| <b>Studies and Analyses</b>                     |  |     |    |  |
| 5   | Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?                          |     |    | Not applicable   |
| 6   | Did the applicant follow the scientific advice provided regarding matters related to dose selection?   |     |    | Not applicable   |
| 7   | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?   |     | X  |  |
| 8   | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? |     |    | Not applicable   |
| 9   | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?   |     |    | Not applicable   |
| 10  | Did the applicant submit all the pediatric exclusivity data, as described in the WR?   |     |    | Sponsor has an agreed iPSP plan.   |
| 11  | Is the appropriate pharmacokinetic information submitted?  | X   |    |  |
| 12  | Is there adequate information on the pharmacokinetics  | X   |    |  |

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 206-538**

|                |  |   |  |                |
|----------------|--|---|--|----------------|
|                | and exposure-response in the clinical pharmacology section of the label?   |   |  |                |
| <b>General</b> |  |   |  |                |
| 13             | On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?                               | X |  |                |
| 14             | Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?                                | X |  |                |
| 15             | On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?   | X |  |                |
| 16             | Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X |  |                |
| 17             | Was the translation from another language important or needed for publication?   |   |  | Not applicable |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

S. W. Johnny Lau, R.Ph., Ph.D.

\_\_\_\_\_  
Reviewing Pharmacologist Date

Lokesh Jain, Ph.D.  
\_\_\_\_\_  
Team Leader Date

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 206-538**

| <b>Office of Clinical Pharmacology</b>  |                           |                             |   |  |
|---|---------------------------|-----------------------------|---|--|
| <i>New Drug Application Filing and Review Form</i>  |                           |                             |   |  |
| <u>General Information about the Submission</u>   |                           |                             |   |  |
|   | Information               |                             | Information                                   |  |
| NDA   | 206-538                   | Brand Name                  | To be determined                              |  |
| OCP Division  | 2                         | Generic Name                | Insulin glargine                              |  |
| Medical Division  | DMEP                      | Drug Class                  | Insulin analog                                |  |
| OCP Reviewer  | S.W. Johnny Lau           | Indication(s)               | Improve glycemic control in diabetes mellitus |  |
| OCP Team Leader   | L. Jain                   | Dosage Form                 | Solution for injection                        |  |
| Date of Submission  | 25-APR-2014               | Dosing Regimen              | Individualized dose, any time once daily      |  |
| Estimated Due Date of OCP Review  | 25-NOV-2014               | Route of Administration     | Subcutaneous                                  |  |
| PDUFA Due Date  | 25-FEB-2015               | Sponsor                     | Sanofi  |  |
| Division Due Date   | 25-JAN-2015               | Priority Classification     | Standard                                      |  |
| <u>Clin. Pharm. and Biopharm. Information</u>   |                           |                             |   |  |
|   | “X” if included at filing | Number of studies submitted | Number of studies reviewed                    | Comments (Study number)                    |
| <b>STUDY TYPE</b>   |                           |                             |   |  |
| Table of Contents present and sufficient to locate reports, tables, data, etc.              | X                         |                             |   |  |
| Tabular Listing of All Human Studies  | X                         |                             |   |  |
| HPK Summary   | X                         |                             |   |  |
| Labeling  | X                         |                             |   |  |
| Reference Bioanalytical and Analytical Methods  | X                         |                             |   |  |
| <b>I. Clinical Pharmacology</b>   |                           |                             |   |  |
| In vivo mass balance:   |                           |                             |   |  |
| In vitro isozyme characterization   |                           |                             |   |  |
| In vitro metabolite identity  |                           |                             |   |  |
| In vitro metabolism inhibition  |                           |                             |   |  |
| In vitro metabolism induction   |                           |                             |   |  |
| In vitro efflux and uptake transporters inhibition:   |                           |                             |   |  |
| P-gp substrate assessment   |                           |                             |   |  |
| In vitro mechanism of uptake in human liver   |                           |                             |   |  |
| In vitro plasma protein binding:  |                           |                             |   |  |
| Blood/plasma ratio:   |                           |                             |   |  |
| Pharmacokinetics (e.g., Phase I) -  |                           |                             |   |  |
| Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses: |                           |                             |   |  |
| Drug-drug interaction studies -   |                           |                             |   |  |
| In-vivo effects <u>on</u> primary drug:   |                           |                             |   |  |
| In-vivo effects <u>of</u> primary drug:   |                           |                             |   |  |
| In-vitro:   |                           |                             |   |  |
| Subpopulation studies -   |                           |                             |   |  |
| ethnicity:  |                           |                             |   |  |
| pediatrics:   |                           |                             |   |  |
| gender & geriatrics:  |                           |                             |   |  |
| renal impairment:   |                           |                             |   |  |
| hepatic impairment:   |                           |                             |   |  |
| <b>PK/PD:</b>   |                           |                             |   |  |
| Phase 1:  | X                         | 4                           |   | PKD11627, TDR11626, PKD12270, and PDY12335 |
| Phase 3:  |                           |                             |   |  |
| <b>PK/PD:</b>   |                           |                             |   |  |
| Phase 2, dose ranging studies:  | X                         | 1                           |   | T1DM – EFC12456                            |
| Phase 3 clinical STUDIES (placebo controlled):  |                           |                             |   |  |

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 206-538

|  |            |   |  |  |
|--|------------|---|--|--|
| Phase 3 clinical STUDIES (active controlled):    | X          | 4   |  | T1DM – PDY12777; T2DM – EFC11628, EFC11629, and EFC12347 |
| Population Analyses -                            |            |   |  |  |
| Meta-analysis:                                   |            |   |  |  |
| NONMEM:  |            |   |  |  |
| <b>II. Biopharmaceutics</b>                      |            |   |  |  |
| Absolute bioavailability:                        |            |   |  |  |
| Bioequivalence studies – traditional design      | X          | 2   |  | PKD10086 and PKD13560                                    |
| Relative bioavailability                         |            |   |  |  |
| alternate formulation as reference:              |            |   |  |  |
| Food-drug interaction studies:                   |            |   |  |  |
| Absorption site                                  |            |   |  |  |
| Dissolution:                                     |            |   |  |  |
| (IVIVC):   |            |   |  |  |
| Bio-wavier request based on BCS                  |            |   |  |  |
| BCS class  |            |   |  |  |
| <b>III. Other CPB Studies</b>                    |            |   |  |  |
| Phenotype studies:                               |            |   |  |  |
| Chronopharmacodynamics                           |            |   |  |  |
| Pediatric development plan                       |            |   |  |  |
| Literature References                            |            |   |  |  |
| QT prolongation assessment                       |            |   |  |  |
| Total Number of Studies                          |            | 11  |  |  |
| <b>Fileability and QBR comments</b>              |            |   |  |  |
|  | "X" if yes |   |  |  |
| Application fileable?                            | X          |   |  |  |
| Comments to be sent to firm?                     |            | <ul style="list-style-type: none"> <li>• Please inform the location of the raw and smoothed datasets (if applicable) for both glucose infusion rate and blood glucose concentration as well as the codes used to generate the smoothed profiles for Studies PKD10086, PKD13560, PKD11627, PKD12270, and TDR11626 or submit these data.</li> </ul> |  |  |
| QBR questions (key issues to be considered)      |            | <ul style="list-style-type: none"> <li>○ To characterize the pharmacokinetic and pharmacodynamic properties of HOE901-U300 and compare with those of insulin glargine.</li> </ul>   |  |  |
| Other comments or information not included above |            |   |  |  |
| Primary reviewer Signature and Date              |            |   |  |  |
| Secondary reviewer Signature and Date            |            |   |  |  |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 206-538

## Filing Memo

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### CLINICAL PHARMACOLOGY

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**NDA:** 206-538 Serial 0000  
**Compound:** Insulin glargine  
**Sponsor:** Sanofi  
**Submission Date:** April 25, 2014  
**Relevant IND:** 112,400  
**From:** S.W. Johnny Lau, R.Ph., Ph.D.

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#### **Background**

The sponsor markets insulin glargine (Lantus<sup>®</sup>; NDA 21-081 approved on April 20, 2000) to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. The sponsor submitted NDA 206-538 Serial 0000 to seek approval of HOE901-U300 for the indication to improve glycemic control in adults with diabetes mellitus. HOE901-U300 has the same composition as the current commercial formulation of Lantus<sup>®</sup> with adjustment of 3-times the amount of active pharmaceutical ingredient and corresponding zinc content. This document concerns the filing review of this original new drug application of HOE901-U300.

#### **Findings**

To support NDA 206-538 Serial 0000, the sponsor submitted studies' results as indicated in the table above. Findings' highlights follow:

- The sponsor claims that the difference between HOE901-U300 and Lantus rests solely in the pharmacokinetic (PK)/pharmacodynamic (PD) profiles of the 2 formulations as shown in the Phase 1 PK/PD clamp studies PKD10086, PKD11627 and in steady state in TDR11626, which showed a flatter and prolonged (up to 36 hours) profile of the insulin concentration and glucose-lowering activity of HOE901-U300 compared with Lantus at matching doses.
- The sponsor conducted Study PKD13560 to assess the bioequivalence between the standard formulation (b) (4) and the formulation (b) (4) of HOE901-U300. The sponsor also conducted 2 PK/PD studies in Japanese patients, namely the Study PKD12270 for single dose and Study PDY12335 for once daily dose for 28 days. See Attachment for further details of the PK/PD and Biopharmaceutics studies.
- The Phase 3 program included 4 pivotal Phase 3 studies to assess the efficacy and safety of HOE901-U300 in patients with T1DM and T2DM; EFC11628, EFC11629 and EFC12347 in T2DM and study EFC12456 in T1DM. These studies were designed as randomized, controlled studies in a broad range of patient populations requiring insulin treatment, including insulin-naïve patients with T2DM not adequately controlled on non-insulin antihyperglycemic agents (EFC12347) or insulin-pretreated T2DM patients, where the basal insulin was given in combination with mealtime insulin (EFC11628) or in combination with oral antihyperglycemic drugs (EFC11629) or patients with T1DM (EFC12456). The comparator in all studies was Lantus (insulin glargine 100 U/mL).
- The sponsor provided bioanalytical validation reports for the measurement of insulin glargine via radioimmunoassay and measurement of insulin glargine and its M1 and M2 metabolites via LC-MS/MS assay. The sponsor also provided the validation report of the measurement of C-peptide via radioimmunoassay.
- The sponsor provided electronic files (.xpt files) for PK and PD measures for the clinical pharmacology trials and efficacy and safety trials.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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- The sponsor provided annotated proposed label for review. As a cursory review for filing, the sponsor provided adequate information for substantive review of the proposed label.

**Attachment starts here.**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 206-538

## Clinical pharmacology studies of HOE901-U300

| Study type   | Study code | Dose or dose range<br>Treatment duration   | Number randomized and treated |
|--|------------|--|-------------------------------|
| <b>Biopharmaceutical studies</b>   |            |  |                               |
| Bioequivalence (PK, PD) of single doses of HOE901-U300 versus Lantus in healthy male and female subjects.  | PKD10086   | 2 replicates of single SC dose of 0.4 U/kg Lantus and HOE901-U300, followed by a 30-hour euglycemic clamp in a 2-treatment, 4-period, 2-sequence crossover design.<br><br>4 days (four 30-hour clamps).  | 24 <sup>a</sup>               |
| Bioequivalence after repeated doses of 2 formulations of HOE901-U300, (b) (4) and cartridge formulation in male and female patients with T1DM.   | PKD13560   | 6 once daily SC doses of 0.4 U/kg HOE901-U300 (b) (4) formulation and HOE901-U300 cartridge formulation in a 2-treatment, 2-period, 2-sequence crossover design.<br><br>12 days (two 6-day periods, 24-hour clamps from Day 6 in each period).   | 50 <sup>b</sup>               |
| <b>Pharmacokinetics and pharmacodynamics in patients (T1DM)</b>  |            |  |                               |
| Comparison of PD and PK of HOE901-U300 versus Lantus, and of dose-response of 3 different single doses of HOE901-U300 in male and female patients with T1DM.                           | PKD11627   | 4 single SC administrations of insulin glargine as HOE901-U300 0.4 (T <sub>1</sub> ), 0.6 (T <sub>2</sub> ), and 0.9 (T <sub>3</sub> ) U/kg and Lantus 0.4 U/kg (R) in a 4-treatment, 4-period, 4-sequence crossover design, each administration followed by a 36-hour euglycemic clamp.<br><br>4 days (four 36-hour clamps).                                  | 24 <sup>c</sup>               |
| Safety and tolerability of repeated doses of HOE901-U300. Comparison of PD and PK of 2 dose levels of HOE901-U300 versus Lantus in steady state in male and female patients with T1DM. | TDR11626   | 8 once daily SC doses of 0.4 U/kg HOE901-U300 compared to 0.4 U/kg Lantus and 0.6 U/kg HOE901-U300 compared to 0.4 U/kg Lantus in a 2-parallel, 2-treatment, 2-period, 2-sequence crossover design, with 36-hour euglycemic clamps starting with the last dosing in each period.<br><br>16 days (two 8-day periods, 36-hour clamps from Day 8 in each period). | 30 <sup>d</sup>               |
| Comparison of the metabolic effect of 2 different single HOE901-U300 doses versus 1 single 0.4 U/kg dose of Lantus in male and female Japanese patients with T1DM.                     | PKD12270   | 3 single SC administrations of insulin glargine, as HOE901-U300 0.4 (T <sub>1</sub> ) and 0.6 (T <sub>2</sub> ) U/kg and Lantus 0.4 U/kg (R) in a 3-treatment, 3-period, 3-sequence crossover design, each administration followed by a 36 hour euglycemic clamp.<br><br>3 days (three 36-hour clamps).  | 18 <sup>b</sup>               |
| Comparison of the 24-hour glycemic profile in continuous glucose monitoring (CGM) after repeated doses between HOE901-U300 and Lantus in male and female Japanese patients with T1DM.  | PDY12335   | Once daily SC doses of HOE901-U300 compared to Lantus in a 2-treatment, 2-period, 2-sequence crossover design, with individual up-titration.<br><br>56 days (two 28-day periods). 24-hour glucose profiles for 3 consecutive days by CGM at pre-treatment, at the end of treatment Period 1 and at the end of treatment Period 2.                              | 20 <sup>b</sup>               |

<sup>a</sup> Healthy subjects; of these, 23 of 24 subjects received HOE901-U300.

<sup>b</sup> Patients with T1DM; all patients received HOE901-U300.

<sup>c</sup> Patients with T1DM; of these 23 of 24 patients received HOE901-U300 and 22 T1DM patients were analyzed for PD and PK.

<sup>d</sup> Patients with T1DM; of these, 29 of 30 patients received HOE901-U300.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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**Overview of Phase 2/3 studies**

| <b>Studies in T1DM</b>           | <b>EFC12456<br/>Phase 3</b>  | <b>PDY12777<br/>Phase 2; Exploratory CGM study</b>   |
|----------------------------------|--|--|
| Population                       | T1DM on basal insulin in combination with mealtime insulin analog  | T1DM on basal insulin in combination with mealtime insulin analog  |
| Region                           | North America, Europe, Japan   | USA  |
| Comparator                       | Lantus   | Lantus   |
| Randomization                    | 1:1:1:1 <ul style="list-style-type: none"> <li>• HOE901-U300 morning injection</li> <li>• HOE901-U300 evening injection</li> <li>• Lantus morning injection</li> <li>• Lantus evening injection</li> </ul> | 1:1:1:1<br>HOE901-U300 injection sequence: <ul style="list-style-type: none"> <li>• Period A morning <math>\text{\AE}</math> Period B evening</li> <li>• Period A evening <math>\text{\AE}</math> Period B morning</li> </ul> Lantus injection sequence <ul style="list-style-type: none"> <li>• Period A morning <math>\text{\AE}</math> Period B evening</li> <li>• Period A evening <math>\text{\AE}</math> Period B morning</li> </ul> |
| Main Objectives                  | Efficacy and safety  | Efficacy and safety  |
| Route<br>Injection device:       | Once daily SC injection<br>HOE901-U300: (b) (4)<br>Lantus: SoloStar  | Once daily SC injection<br>HOE901-U300 and Lantus:<br>Half-unit U100 (b) (4); whole-unit<br>U100 (b) (4) for Lantus doses >30 units  |
| Duration of treatment            | 6 months (main study period)<br>6 months comparative extension period <sup>a</sup>   | 16 weeks (2 x 8 weeks)   |
| Number of patients<br>randomized | HOE901-U300: 274<br>Lantus: 275  | HOE901-U300: 30<br>Lantus: 29  |

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 206-538

| Studies in T2DM               | EFC11628<br>Phase 3  | EFC11629<br>Phase 3  | EFC12347<br>Phase 3  |
|-------------------------------|--|--|--|
| Population                    | T2DM on basal insulin in combination with mealtime insulin analog  | T2DM on basal insulin in combination with OAD  | Insulin-naïve T2DM not adequately controlled on non-insulin AHA                    |
| Region                        | North America, South America, Europe, South Africa   | North America, South America, Europe, South Africa   | North America, Europe, Japan   |
| Comparator                    | Lantus   | Lantus   | Lantus   |
| Randomization                 | 1:1  | 1:1  | 1:1  |
| Main Objectives               | Efficacy and safety  | Efficacy and safety  | Efficacy and safety  |
| Route<br>Injection device     | Once daily SC injection<br>HOE901-U300:<br>modified Solostar<br>Lantus: Solostar   | Once daily SC injection<br>HOE901-U300:<br>modified Solostar<br>Lantus: Solostar   | Once daily SC injection<br>HOE901-U300:<br>(b) (4)<br>Lantus: Solostar             |
| Duration of treatment         | 6 months (main study period)<br>6 months comparative extension period <sup>a</sup>   | 6 months (main study period)<br>6 months comparative extension period <sup>a</sup>   | 6 months (main study period)<br>6 months comparative extension period <sup>a</sup> |
| Number of patients randomized | HOE901-U300: 404<br>Lantus: 403  | HOE901-U300: 404<br>Lantus: 407  | HOE901-U300: 439<br>Lantus: 439  |
| <b>3-month substudies</b>     |  |  | NA   |
| Patient population:           | Patients randomized and treated with HOE901-U300 during the main study period  | Patients randomized and treated with HOE901-U300 during the main study period  |  |
| Comparison                    | HOE901-U300 injection intervals <ul style="list-style-type: none"> <li>• at fixed 24-hour intervals</li> <li>• at intervals of 24±3 hours</li> </ul> | HOE901-U300 injection intervals <ul style="list-style-type: none"> <li>• at fixed 24-hour intervals</li> <li>• at intervals of 24±3 hours</li> </ul> |  |
| Randomization                 | 1:1  | 1:1  |  |
| Objective:                    | Efficacy and safety  | Efficacy and safety  |  |
| Duration:                     | 3 months (Month 6 – Month 9 extension period)  | 3 months (Month 6 – Month 9 extension period)  |  |
| Number of patients randomized | Fixed intervals: 53<br>Adaptable intervals: 56   | Fixed intervals: 44<br>Adaptable intervals: 45   |  |

<sup>a</sup> Extension period ongoing at the time of the dossier cut-off date; results of safety extension periods not included in the dossier

OAD = oral antihyperglycemic drugs; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; CGM = continuous glucose monitoring;  
NA = not applicable

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SZE W LAU  
06/13/2014

LOKESH JAIN  
06/13/2014