Study Results Summary for Public Disclosure – Interventional Studies

QU-FOR-0055625

Sponsor: Sanofi **Drug substance(s):** HOE901-U300 (Insulin Glargine 300 U/mL)	**Study Identifiers:** Universal Trial Number (UTN): U1111-1272-6776 Investigational New Drug (IND) number: 112400 National Clinical Trial (NCT) number: NCT05552859 EudraCT Number: 2022-001485-35 **Study code:** LPS17007

Title of the study:

A 24-Week, Multicenter, Randomized, Open-Label, Parallel-Group Trial Comparing the Efficacy and Safety of Insulin Glargine 300 U/mL (Gla-300) and Insulin Degludec 100 U/mL (IDeg-100) in Insulin-Naïve People with Type 2 Diabetes Mellitus and Renal Impairment: TRENT Trial

Study center(s):

Multicenter trial conducted at 68 sites in the United States (32), Serbia (6), Poland (18), Hungary (6), and Czech Republic (6)

Study period:

Date first study participant enrolled: 05 Dec 2022

Date last study participant completed: 04 Aug 2023

Study Status: Early Discontinuation, a strategic Sponsor's decision due to significant recruitment delay and a small sample size recruited. No safety signals were detected during the trial, and the trial team remained blinded to the data collected for the randomized participants at the time of early discontinuation of the trial.

Phase of development: 4

Objectives:

Primary: To demonstrate noninferiority (with a margin of 0.3%) and, if achieved, to demonstrate superiority in the efficacy of Gla-300 compared with IDeg-100 in terms of change in HbA1c from baseline to Week 24 in insulin-naïve people with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA.

Secondary; To evaluate the effects of treatment with Gla-300 compared with IDeg-100 on the clinical parameters.

Safety: To assess the safety and tolerability of Gla-300 and IDeg-100.

Methodology:

LPS17007 was a multicenter, multinational, randomized, open-label, parallel group clinical trial designed to compare the efficacy and safety of Gla-300 and IDeg-100 in insulin-naïve people with type 2 diabetes mellitus (T2DM) and renal impairment.

At baseline (Day 0, Visit 2), all participants were randomly assigned in a 1:1 ration to 1 of 2 treatment groups: the Gla-300 group and the IDeg-100 group.

Participants were allowed to continue their current treatment with oral antidiabetic drugs (OADs) with or without a glucagon-like peptide-1 receptor agonist (GLP-1 RA; oral or injectable; with stable dose for ≥3 months) throughout the trial period unless such treatment had to be stopped or modified for safety reasons.

The trial consisted of a screening period of up to 2 weeks; a 24-week open-label treatment period, including a titration period' and a 7-day posttreatment safety follow-up period. The maximum trial duration per participant was 27 weeks. Five site visits and at least 13 phone contacts were scheduled. During the titration period, the doses of Gla-300 and IDeg-100 were adjusted using a recommended dose-adjustment algorithm.

Efficacy parameters, including glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and 7-point self-measured plasma glucose (SMPG), were assessed. Safety parameters, such as adverse events (AEs) and serious adverse events (SAEs), including adverse events of special interest (AESIs), hypoglycemia events, and other safety evaluation were assessed.

The abbreviated clinical study report (CSR) provides data on the primary efficacy endpoints (mean change from baseline to Week 24 in HbA1c level), secondary efficacy endpoints (mean change from baseline in FPG level , SMPG values, 7-point SMPG profiles, and the percentage of participants who reached HbA1c target of <7.0% at Week 24), and safety (incidence of AEs, SAEs [including AESIs], death, and hypoglycemic events) collected up to 18 Oct 2023 (i.e. database lock date).

Since the trial was terminated prematurely due to recruitment delay, and the resulting small sample size, some of the safety endpoints, exploratory endpoints, and endpoints related to the CGM substudy were not obtained for this trial. Therefore, their results are not included in this abbreviated CSR.

Number of study participants:

Planned: 630 participants (315 per treatment group)

Enrolled/Randomized: 62 participants (31 per treatment group)

Treated: 62 participants (31 per treatment group)

Evaluated:

Efficacy: 62 participants (31 per treatment group)

Safety: 62 participants (31 per treatment group)

Diagnosis and criteria for inclusion:

Participants who met all of the inclusion criteria and none of the extension criteria were planned to be enrolled into the trial.

Key inclusion criteria:

- Adults aged ≥18 years at screening,
- Diagnosed with Type 2 Diabetes Mellitus (T2DM) of >1-year duration and with glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable) at stable doses for ≥3 months before screening period;
- Had HbA1c≥7.5% and ≤10.5% at screening;
- With renal impairment, as defined by the estimated glomerular filtration rate (eGFR) of <660 mL/min/1.73 m^2 and ≥15 mL/min/1.73m^2;
- Had adequately controlled blood pressure with stable antihypertensive therapy at trial inclusion;
- Was insulin-naïve, except for short use of insulin not exceeding 15 days during the last year before the screening period;
- Was capable of understanding the written informed consent, and provides signed written informed consent;
- Was willing and able to complete the electronic diary (eDiary) and agrees to comply with protocol requirements;
- Was willing and able to fast without having administered study drug for scheduled site visits.
- Key exclusion criteria:Had initiated treatment with potential novel therapies like dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA;
- Had a body mass index (BMI) >45 kg/m^2 during the screening period;
- Had a history of hypoglycemia;
- Had a history of 2 or more episodes of severe hypoglycemia and/or 2 or more episodes of diabetic ketoacidosis within the 6 months before the day of screening;
- Had been exposed to other investigational drug(s) within 1 month or 5 half-lives from screening, whichever is longer.

Study products

Investigational medicinal product(s): Gla-300

Formulation/Form & composition: insulin glargine 300 U/mL solution for injection in prefilled (disposable) pen (SoloStar®);

Route(s) of administration: subcutaneous (SC) injection, self-administered

Dose regimen: Gla-300 was administrated with recommended starting dose of 0.2 U/kg of body weight once daily. During the treatment the dose was titrated until the participant attained a target fasting SMPG of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. Gla-300 dose was adjusted with recommended dose-adjustment algorithm.

Investigational medicinal product(s): IDeg-100

Formulation/Form & composition: insulin degludec 100 U/mL solution for injection in prefilled (disposable) pen (FlexTouch®)

Route(s) of administration: subcutaneous (SC) injection, self-administered

Dose regimen: IDeg-100 was administrated with recommended starting dose of 10 U once daily. During the treatment the dose was titrated until the participant attained a target fasting SMPG of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. IDeg-100 dose was adjusted with recommended dose-adjustment algorithm.

Duration of treatment/participation: The maximum duration of treatment per participant was 24 weeks.

Duration of observation: a 7-day, post-treatment, safety follow-up period after the last dose of the study drug or after premature/permanent discontinuation from study drug treatment.

Criteria for evaluation

Efficacy:

Primary efficacy end point:

- Difference in the mean change of the HbA1c from baseline to Week 24 (Gla-300 vs IDeg-100)

Secondary efficacy end points:

- Fasting plasma glucose (FPG): Change from baseline to Week 24
- Fasting SMPG: Change from baseline to Week 24
- 7-point SMPG profiles: Change from baseline to Week 24, per time point within 24-hour period
- Percentage (%) of patients reaching HbA1c target of <7.0% at Week 24

Safety: Safety evaluation during the 24-week treatment period, during the titration period, and during maintenance period of:

- All hypoglycemic events
- The frequency of and diurnal distribution (all day, daytime, and nocturnal) of hypoglycemia by category (symptomatic, asymptomatic, severe) per the ADA/EASD hypoglycemia classification
- Local tolerability at injection site
- Hypersensitivity reactions
- AEs and SAEs, including AESIs, and other safety evaluations, including vital signs and body weight

Statistical methods:

The results for the primary endpoint are presented descriptively only, and no formal hypotheses testing was conducted. Primary and all secondary endpoints were analysed for the ITT set. All safety analyses were performed on the safety set. Intention-to-treat [ITT] and safety sets comprised of 62 participants (n=31 per treatment group).

Summary Results:

Population characteristics:

In total, 182 participants were screened for eligibility; of these, 120 participants were screen failures. Among the excluded participants, 106 (58.2%) did not meet the inclusion criteria, whereas 3 (1.6%) did not meet the exclusion criteria. The most common reasons for participants being excluded from the trial were as follows: not having an eGFR of <60 mL/min/1.73m^2 and ≥15 mL/min/1.73m^2 (n=65 [35.7%]), followed by not having an HbA1c ≥7.5% and ≤10.5% at screening (n=51 [28.0%]) and not willing and unable to complete the eDiary and not complying with protocol requirements (n=5 [2.7%]).

The number of randomized participants remained significantly lower (<10%) than was originally planned (i.e., 62 participants were enrolled out of the planned sample size of 630). Consequently, the estimated results were delayed by several years. Hence, sponsor made the strategic decision to discontinue the trial due to this significant recruitment delay. A total of 62 participants were randomized and exposed to Gla-300 (n=31) or IDeg-100 (n=31). Ten participants were eligible for enrollment but considered screen failures due to the sponsor's decision to terminate the trial early. After the discontinuation of the trial, no new participants were enrolled into the trial. However, the participants who were already on the study treatment were assessed using the procedure that had been planned for the last dosing day of the study treatment and were followed up for the completion of any further evaluations that were necessary. One participant (3.2%) in each treatment group completed the 24-week trial treatment period and the trial period as per the protocol. These participants were permanently discontinued from the study drug treatment.

In both treatment groups, the only reported reason for permanent study drug discontinuation was "Other" (the instructed response for discontinuation due to early discontinuation of the trial by the sponsor) (30 [96.8%] each). In both treatment groups, the most common reason for trial discontinuation was trial termination by the sponsor (29 [93.5%] each).

Overall, 54 participants (87.1%) (IDeg-100: 26 [83.9%]; Gla-300: 28 [90.3%]) had at least one significant protocol deviation during the trial period. Two participants were reported for a significant protocol deviation under the category of missing endpoint assessments for the following reason: Laboratory samples at Week 12 were mistakenly not collected, as the investigator had overlooked the list of assessments required at this visit.

Demographics and Baseline Characteristics

Overall, the mean (SD) age of participants was 71.5 (7.5) years. The majority of participants were ≥65 years of age (50 [80.6%]). The proportions of males and females were the same (31 [50.0%] each). The majority of participants were Caucasian (56 [93.3%]) and not Hispanic or Latino (54 [87.1%]).

Overall, the mean (SD) HbA1c level was 8.4% (0.72), and most participants had HbA1c levels <8.5% (39 [62.9%]). The mean (SD) FPG level was 166.7 (32.38) mg/dL, and the mean (SD) SMPG level was 159.6 (38.90) mg/dL. The mean (SD) eGFR was 46.7 (10.4) mL/min/1.73m^2, and most of the participants had an eGFR ≥45 mL/min/1.73m^2 (38 [61.3%]).

Overall, metformin was the most frequently received antihyperglycemic therapy (43 participants [69.4%]). The mean (SD) age at diabetes diagnosis was 57.5 (8.8) years, and the mean (SD) duration of diabetes (time since diagnosis) was 14.6 (7.8) years. None of the randomly assigned participants had a history of gestational diabetes.

A similar trend was observed for HbA1c data expressed in mmol/mol and FPG and SMPG data expressed in mmol/L.

The participant demographic and baseline disease characteristics were mostly similar between the 2 treatment groups.

Efficacy:

Efficacy parameters, including glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and 7-point self-measured plasma glucose (SMPG), were assessed. Since the trial was terminated early as a result of significant recruitment delays and a small sample size, some of the initially set endpoints were not obtained for this trial.

As <10% of the originally planned sample size was enrolled, data from only a small number of participants (n=9 in the IDeg-100 group and n=8 in the Gla-300 group) were available within the analysis window for Week 24. Hence, the results for the primary endpoint are presented descriptively only, and no formal hypotheses testing was conducted. For this abbreviated CSR, analyses of the primary and secondary efficacy endpoints are based on the intention-to-treat (ITT) set.

Primary Efficacy Results:

The mean (SD) HbA1c (%) decreased from baseline to Week 24 in both treatment groups (IDeg-100: -1.0 [0.98]; Gla-300: -0.4 [1.73]). (Note: One participant [3.2%] in each treatment group had unexpectedly high HbA1c values (i.e., increase from baseline to Week 24) IDeg-100: 1.1 absolute [baseline: 7.7; Week 24: 8.8] and Gla-300: 3.5 absolute [baseline: 8.9; Week 24: 12.4].)

A sensitivity analysis was conducted to assess the impact of data from the 2 participants (1 in each treatment group) who had unexpectedly high HbA1c values (i.e., increase from baseline to Week 24). The results of the mean change in HbA1c (%) from baseline to Week 24 showed a similar trend to the primary analysis (IDeg-100: -1.3; Gla-300: -0.9).

The results of subgroup analyses of the primary endpoint showed similarity with the results of the primary efficacy analysis for the following subgroups; however, a meaningful comparison was not possible because of the small sample size:

- Age (<65 years, ≥65 years)
- Sodium-glucose co transporter 2 inhibitor (SGLT-2i) use (yes, no)
- GLP-1 RA use (yes, no)
- Sulfonylurea (SU) use (yes, no)
- eGFR (<45 mL/min/1.73m^2, ≥45 mL/min/1.73 m^2; 15 to <30 mL/min/1.73m^2; 30 to <45 mL/min/1.73m^2; 45 to 60 mL/min/1.73m^2)
- Baseline HbA1c (<8.5%, ≥8.5%)

Secondary Efficacy Results:

Change in FPG from Baseline to Week 24: The mean (SD) FPG (mg/dL) decreased from baseline to Week 24 in both treatment groups (IDeg-100: -55.5 [22.67]; Gla-300: -36.4 [25.16]). A similar trend was observed for FPG data expressed in mmol/L.

Change in Fasting SMPG from Baseline to Week 24: A meaningful comparison of the mean (SD) change in fasting SMPG (expressed in both mg/dL and mmol/L) was not possible because of the small sample size in both treatment groups, especially at Week 24.

Change in the 7-Point SMPG Profile from Baseline to Week 24: A meaningful comparison of the mean (SD) change in the 7-point SMPG profile (expressed in both mg/dL and mmol/L) at 7 time points within a 24-hour period was not possible because of the small sample size in both treatment groups, especially at Week 24.

Percentage of Participants Who Reached the HbA1c Target of <7.0% at Week 24:

A meaningful comparison of the proportion of participants who reached the HbA1c target of <7.0% at Week 24 was not possible because of the small sample size in both treatment groups.

No exploratory efficacy endpoints were derived for the final analysis as the sponsor made a strategic business decision to discontinue the trial due to a significant recruitment delay.

Safety results:

All safety analysis were performed on the safety set.

In total, 7 participants (22.6%) in the IDeg-100 group reported 16 treatment-emergent adverse events (TEAEs) and 5 participants (16.1%) in the Gla-300 group reported 6 TEAEs during the trial period. Treatment-emergent SAEs and treatment-related TEAEs were each reported by at least 3 participants (9.7%) in the IDeg-100 group and 1 participant (3.2%) in the Gla-300 group.

Infections and infestations were the most frequently reported TEAE (that occurred in >1 participant) in any treatment group by system organ class (SOC; IDeg-100: 5 participants [16.1%], 7 events; Gla-300: 2 participants [>6.5%], 2 events).

Three participants (9.7%) in the IDeg-100 group reported 4 TEAEs (hypoglycemic events), and 1 participant (3.2%) in the Gla-300 group reported 1 TEAE (chest discomfort) that were assessed by the investigator as related to the study drug during the trial period.

One participant (0.5%) in the IDeg-100 group died during the trial due to hypertensive heart disease (as per the death certificate) after reportedly being a passenger in a major car accident. The event was not considered to be related to study drug treatment by the investigator and not reportable by the sponsor based on a causality assessment. This event was also considered an AE that led to trial discontinuation.

Four participants reported treatment-emergent SAEs during the trial period: 3 participants (9.7%) in the IDeg-100 group had 5 treatment-emergent SAEs (hypoglycemia, retinal artery occlusion, pulmonary edema, hypertensive heart disease, and cardiac failure congestive), and 1 participant (3.2%) in the Gla-300 group had 1 treatment-emergent SAE (circulatory collapse). Except for hypoglycemia, none of these events were considered related to the study drug treatment by the investigator. Except for the hypertensive heart disease event (i.e., death due to a car accident), none resulted in trial discontinuation.

Nine participants (29.0%) in the IDeg-100 group reported 43 hypoglycemic events, and 11 participants (35.5%) in the Gla-300 group reported 67 hypoglycemic events; almost all of these events (IDeg-100 group: 43; Gla-300 group: 66) were reported during the treatment period (Week 1 to Week 24). Among the events that occurred during the treatment period, the majority were reported during the titration period (Week 1 to Week 12) (IDeg-100 group: 36; Gla-300 group: 41) compared to the maintenance period (Week 12 to Week 24) (IDeg-100 group: 7; Gla-300 group: 25). In both treatment groups, most events were confirmed by the American Diabetes Association (ADA) criteria (IDeg-100: 9 [29.0%], 40 events; Gla-300: 11 [35.5%], 63 events). One participant (3.2%) in the IDeg-100 group reported an ADA Level 3 event (1 event), whereas no one in the Gla-300 group reported such events.

Issue date: 18 Jul 2024