STATISTICAL ANALYSIS PLAN

Protocol title:	**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**
Protocol number:	**LPS17007**
Compound number (INN/Trademark):	**HOE901-U300 (Insulin Glargine 300 U/mL)**
Study phase:	**Phase 4**
Short title:	**Gla-300 and IDeg-100 in Insulin-Naïve People with Type 2 Diabetes Mellitus and Renal Impairment**
Statistician:	PPD PPD
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TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This statistical analysis plan (SAP) for study LPS17007 is based on the protocol dated 28 April 2022. There are no major changes to the statistical analysis features in this SAP.

The first participant was randomized on 20 December 2022.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	17-Oct-2023	Not Applicable	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

This is a multicenter, multinational, randomized, open-label, parallel-group clinical trial comparing the efficacy and safety of second-generation basal insulin analogs, insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL (IDeg-100), in insulin-naïve participants with type 2 diabetes mellitus (T2DM) and renal impairment who have glycemic levels above target with oral antidiabetic drugs (OADs) with or without glucagon-like peptide 1 receptor agonist (GLP-1 RA [oral or injectable]), defined as a glycated hemoglobin (HbA1c) level of ≥7.5% and ≤10.5% and an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 and ≥15 mL/min/1.73 m^2 at screening. As Gla-300 and IDeg-100, the control drug, are distinguishable, this trial is an open-label design, and no attempt will be made to blind administration from the patients and the physicians. However, the team in charge of statistical analysis plan and programming of analyses, and of data review that occur before database lock, will be blinded from treatment allocation. Study drug titration review will also be performed by dedicated and qualified unblinded persons.

The trial will be conducted in approximately 630 participants. At baseline (Day 0, Visit 2), participants will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms: Gla-300 arm or IDeg-100 arm and will initiate their study drug treatment. Randomization will be stratified by HbA1c value at screening (<8.5%, ≥8.5%), SU (sulfonylureas) use (Yes, No), and eGFR (<45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2). Participants will be allowed to continue their current treatment with OADs with or without glucagon-like peptide-1 receptor antagonist (GLP-1RA) (oral or injectable; with stable doses for ≥3 months) throughout the trial period unless such treatments must be stopped or modified for safety reasons.

During the titration period (ie, from Week 1 through Week 12), the doses of Gla-300 and IDeg-100 will be adjusted using a recommended dose-adjustment algorithm. After randomization, the dose will be titrated at least weekly (but no more than every 3 days), until the participant reaches a target fasting self-measured plasma glucose (SMPG) value of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. Dose adjustments will be based on a median of fasting SMPG values from the last 3 measurements, including the value on the day of titration, measured by the participant using glucose meters and accessories supplied by the sponsor through a vendor. Best efforts should be made to reach the glycemic target by 8-12 weeks after randomization.

The maximum trial duration per participant will be 27 weeks. Five site visits and at least 13 phone contacts are scheduled, as well as an unscheduled phone contact (during the treatment period) for study drug resupply, if required. A participant will be considered to have completed the trial if they have completed all phases of the trial, including the last visit (Week 25 follow-up phone contact).

CCI [redacted]

CCI [redacted]

The study was early terminated by the Sponsor on 27 June 2023 (hereinafter referred to as "early termination"). Early termination by Sponsor was due to severe recruitment delay. There are no safety signals detected, and the study team remained blinded to the data collected for the randomized subjects at the time of early termination decision.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate non-inferiority (with a margin of 0.3%) and, if achieved, to demonstrate the 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 participants with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA	• HbA1c level: Change from baseline to Week 24
Secondary	
• To evaluate the effects of treatment with Gla-300 compared with IDeg-100 on the clinical parameters • To assess the safety and tolerability of Gla-300 and IDeg-100	• 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 participants reaching HbA1c target of <7.0% at Week 24 • Safety evaluations of the following (during the 24-week treatment period, during the titration period, and during the maintenance period): - All hypoglycemia events - The frequency of and diurnal distribution (all day, daytime (occurring between 06:00 and 23:59 inclusively), and nocturnal (occurring between 00:00 and 05:59 inclusively) of hypoglycemia by category (symptomatic, asymptomatic, severe) per the ADA/EASD hypoglycemia classification - Local tolerability at injection site - Hypersensitivity reactions - Adverse events (AEs) and serious adverse events (SAEs), including AESIs, and other safety evaluations, including vital signs and body weight

Objectives	Endpoints
Exploratory	
[redacted] CCI	
[redacted] CCI	

Objectives	Endpoints
CCI	

1.2.1 Estimands

The primary estimands defined for the main endpoint are summarized in below Table 3. More details are provided in Section 4.

For each of these estimands, the comparison of interest will be the comparison of Gla-300 versus IDeg-100.

Table 3 - Summary of primary and supplementary estimands for main endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To demonstrate non-inferiority (with a margin of 0.3%) and, if achieved, to demonstrate the 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 participants with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA				
Primary endpoint (Estimand 1a: treatment policy, primary)	Change in HbA1c level from baseline to Week 24	Intent-to-treat	Regardless of discontinuation of study drug treatment due to any reasons[a] / regardless of use of rescue therapies (treatment policy)	Missing data to be handled using a multiple imputation (MI) strategy dependent upon treatment-completion status[a]. An ANCOVA model that includes baseline HbA1c value as a covariate and study drug treatment and stratification factors at randomization (other than categorized HbA1c) as fixed factors to be implemented for each imputed dataset. The mean difference between treatment arms (Gla-300 vs IDeg-100) will be estimated based on the least-squares (LS) means in the ANCOVA model. Estimated differences and their SEs will be combined across imputed data sets to produce a single point estimate and CI using Rubin's rules and presented with a 2-sided 95% CI and p-value.
Primary endpoint (Estimand 1b: hypothetical strategy, supplementary)	Change in HbA1c level from baseline to Week 24	Intent-to-treat	Assuming no discontinuation of study drug treatment due to any reasons and use of rescue therapies (hypothetical strategy)[b]	A mixed-effect model with repeated measures (MMRM) to be performed for Hb1Ac values at Week 12 and Week 24 that includes study drug treatment, visit, and stratification factors at randomization (other than categorized HbA1c) as fixed factors, baseline HbA1c value as a covariate and treatment-by-visit and baseline HbA1c value-by visit-interactions. Least-squares (LS) means and differences with 95% CIs and p-values to be presented. This estimand is only to be estimated to support non-inferiority.

a Missing data from participants discontinuing the study drug treatment will be imputed using data from participants also discontinuing the study drug treatment but who have their endpoint assessed within each treatment arm. Missing data from participants completing the 24-week treatment period will be imputed using a model estimated from data observed in other participants completing the study drug treatment within each treatment arm.

b Data collected after discontinuation of study drug treatment due to any reasons or after use of rescue therapies will be considered as missing in the analysis of change from baseline to Week 12 and Week 24 in HbA1c level (Gla-300 vs IDeg-100).

2 SAMPLE SIZE DETERMINATION

A total sample size of 566 participants (283 per treatment arm with a 1:1 allocation ratio) was determined to demonstrate non-inferiority of Gla-300 versus IDeg-100 with 90% power and 2.5% 1-sided significance level based on the following assumptions on the primary endpoint:

- True mean difference in change from baseline to Week 24 in HbA1c level of 0 between Gla-300 and IDeg-100.
- Common standard deviation (SD) of 1.1%.
- Non-inferiority margin on the mean difference of 0.3%.

The non-inferiority margin was chosen based on the European Medicines Agency (EMA) guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (1).

Assuming a 10% dropout rate, a total of 630 participants will be randomized (315 per treatment arm).

For showing the superiority of Gla-300 to IDeg-100 the power will be at least 90%, assuming the true difference in the mean change between Gla-300 and IDeg-100 is ≤-0.3%.

Calculations were made using nQuery Software Version 7.0.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 4 - Populations for analyses

Population	Description	Analyses
Screened	All participants who signed the informed consent form (ICF).	Participant disposition analyses.
Safety	All randomized participants who receive at least 1 dose of study drug treatment. All analyses using the safety set will be done according to the treatment actually received.	Safety analyses.
Intent-to-treat (ITT)	All participants who sign the ICF and are randomized into the trial. All analyses using the ITT set will group participants according to their randomized treatment.	Primary endpoint analyses (including subgroup analyses), secondary endpoints analyses, exploratory endpoints analyses not related to the CGM substudy, demographics analyses, baseline characteristic analyses, participant disposition analyses.
Per-protocol (PP)	All randomized participants who complete the trial without significant protocol deviations impacting the primary endpoint.	Supportive analysis of the primary endpoint analysis.
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Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the as-randomized intervention group if the participant has received at least one administration of the as-randomized intervention.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

Due to early termination of the study, the analyses described in this SAP were not performed in totality due to lack of data and in accordance with the abbreviated CSR (clinical study report). See Appendix 2 (Section 5.2): Changes to protocol-planned analyses for additional details.

In general, continuous data will be summarized using the number of observations available, mean, SD, median, Q1, Q3, minimum, and maximum.

All mean, SD, median, Q1 and Q3 values will be formatted to one more decimal place than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value.

Categorical data will be summarized using frequency counts and percentage of participants. When count data are presented, the percent will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted 'Missing' will be included in count tabulations for demographics, baseline characteristics and compliance to account for missing values. No percentages will be displayed on the 'Missing' rows and the percentages on the other rows will be based on the number of non-missing observations. Unless otherwise specified, the denominator for all other percentages will be the number of participants in that treatment within the specific analysis set of interest. All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses. When the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0), unless otherwise specified.

All CIs presented will be 2-sided 95% CIs, unless otherwise specified, and will be displayed to the same level of precision as the statistic they relate to. If an estimate or a CI is not estimable, it will be presented as 'NE'. If neither an estimate, nor its CI are estimable, it will be presented as simply 'NE', not displaying 'NE' twice.

The p-values will be rounded to four decimal places. If a p-value is less than 0.0001 it will be reported as '<0.0001'. If a p-value is greater than 0.9999 it will be reported as '>0.9999'. The baseline value is defined as the last available non-missing value before the first injection of study drug (Gla-300 or IDeg-100). For participants randomized but not treated, the baseline value is defined as the last available non-missing value recorded before randomization occurs at the end of the screening period. Where time is collected, it will be included in the determination of baseline records. Any measurement or assessment recorded on the day of first dose administration of open-label IMP (or day of randomization for participants randomized but not treated) with missing assessment time will be considered as Baseline.

If multiple valid values of a variable (efficacy or safety) occur within the same day considered as Baseline (and the recorded times of measurement do not identify which of them is the latest assessment), the following rules will be considered:

- If only one of the multiple valid values was measured during a scheduled visit, it will be considered as Baseline in the analysis.

- If multiple values are measured during a scheduled visit within the same day, then these values will be averaged, and the average will be considered as Baseline for the analysis. If there are also values within the same day not collected during a scheduled visit, these will be excluded from the average.
- If no values measured within the same day were assessed during a scheduled baseline, then all measurements from that day will be averaged, and this value will be considered as Baseline for the analysis.

A stepwise closed testing approach will be used for the primary efficacy endpoint to assess non-inferiority and superiority sequentially.

- Step 1 will assess non-inferiority of Gla-300 versus IDeg-100. To assess non-inferiority, the 2-sided 95% CI of the difference in the mean change from baseline to Week 24 in HbA1c level between Gla-300 and IDeg-100 in the ITT population will be compared with the predefined non-inferiority margin of 0.3%. Non-inferiority will be demonstrated if the 2-sided 95% CI of the difference in the mean change from baseline to Week 24 in HbA1c level between GLa-300 and IDeg-100 lies entirely below 0.3% (equivalent to a 1-sided test at the 2.5% significance level).
- Step 2 will test superiority of Gla-300 versus IDeg-100 if noninferiority of Gla-300 versus IDeg-100 as described above has been demonstrated. The superiority of Gla-300 versus IDeg-100 will be established if the 95% CI for the difference in mean change from baseline to Week 24 in HbA1c level between Gla-300 and IDeg-100 lies entirely below 0%. If non-inferiority has been established but the superiority is not met, the declaration of non-inferiority will be further supported by a supplementary estimand as described in Section 4.3.4.

There is no multiplicity argument that affects switching between non-inferiority and superiority in the analysis of the primary endpoint, since both are based on the same estimand and it therefore corresponds to a simple closed testing procedure. If superiority for the primary endpoint (change from baseline to Week 24 in HbA1c level) is achieved, secondary endpoints will be assessed for superiority and adjusted for Type I error related to multiple testing using the Holm procedure as described in Section 4.6. Control of Type I error will be limited to the primary and key secondary efficacy endpoints for the overall population. No statistical claim will be made on the exploratory efficacy endpoints (including the CGM substudy endpoints), nor for subgroup analyses.

All safety analyses will be performed on the safety set.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and absolute change from baseline) by analysis visits will be provided on observed cases (OC; ie, inclusion of only participants having non-missing assessments for a specific analysis visit). Descriptive summaries of continuous efficacy and safety data at baseline will be included when presenting descriptive summaries of the corresponding changes from baseline, where appropriate. Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).
Despite the open-label administration of the study drugs, all statistical analyses outlined in this plan prior to final database lock will be developed and performed blindly. A process will be

applied to ensure blinding of Gla-300 and IDeg-100 administrations and any potentially unblinding information.

All statistical analyses will be performed using SAS software Version 9.4 or higher.

Observation period

The observation period will be divided into 3 segments for non-safety analyses:

- The **pre-treatment period** (up to 2 weeks) is defined as the time between the date of signed informed consent and the first injection of the open-label study drug.
- The **on-treatment period** (24-weeks) is defined as the 24-week open-label treatment period. The on-treatment period includes a 12-week titration period where study drug doses will be adjusted using a recommended dose-adjustment algorithm, as well as a 12-week maintenance period at the titrated dose.
- The **post-treatment period** is defined as the 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.

The on-study period is defined as the time from the date of signed informed consent until the end of the study defined as the last scheduled visit for those who completed the study and the end-of-study date ("Status Date") collected on electronic case report form (eCRF) page "Completion of End of Study" for those who did not complete the study. If death is the end-of-study reason, date of death will be used.

The observation period used for safety analyses is described in Section 4.7.

The maximum trial duration per participant will be 27 weeks.

4.2 PARTICIPANT DISPOSITIONS

The number of participants included in each of the analysis populations listed in Table 4 will be summarized. Percentages for the PP population and CGM Substudy population will be calculated using the ITT set as the denominator.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number of participants screened, the number (%) of screen failures, and number (%) of reason for screen failures will be summarized for the screened set.

The number (%) of participants in the following categories will also be provided, using the ITT (randomized population) as the denominator:

- Randomized and not exposed participants.
- Randomized and exposed participants.
- Participants who completed the 24-week study treatment period as per protocol.
- Participants who did not complete the 24-week study treatment period as per protocol and main reason for permanent intervention discontinuation.

- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

The number of exposed and not randomized participants will also be included in the summary above.

In addition, the number (%) of participants screened, screened-failed, randomized, randomized and exposed, with study drug discontinuation and with study discontinuation will be provided by country and site. For the number (%) of participants screened and screen-failed, the screened set will be used as a denominator; for the remaining summaries, the ITT set will be used as the denominator for percentages.

The number (%) of participants with trial impacts (disruptions) due to coronavirus disease 2019 (COVID-19) will also be summarized for the safety set. Participants for whom at least one of the following events occurred during the study will be presented:

- Permanent discontinuation of treatment due to COVID-19, defined as participants whose "Main Reason for Premature End of Treatment" on End of Treatment eCRF page is "Adverse Event", and a corresponding adverse event (AE) of "Covid-19" with "Drug withdrawn" as the response to "Action Taken with Study Treatment" on the Adverse Events eCRF page.
- Permanent discontinuation of treatment due to AE related to COVID-19 infection, defined as participants whose "Main Reason for Premature End of Treatment" on End of Treatment eCRF page is "Adverse Event", and a corresponding adverse event of "AE Term due to Covid-19" with "Drug withdrawn" as the response to "Action Taken with Study Treatment" on the Adverse Events eCRF page.
- Premature end of treatment due to COVID-19 pandemic, defined as participants whose "Main Reason for Premature End of Treatment" on the End of Treatment eCRF page is "Other", and in "If Other, specify" beginning the Specify comment following text "Covid-19:".
- Premature end of study due to COVID-19 pandemic, defined as participants whose "Subject Status" on the Completion of End of Study eCRF page is "Other", and in "If Other, specify details" beginning the Specify comment following text "Covid-19:".

Protocol deviations

Significant protocol deviations (automatic or manual), including drug dispensing irregularities, will be summarized for the ITT population. Protocol deviations due to the COVID-19 pandemic will be categorized as such. Protocol deviations will come from the clinical trial management system and will be categorized according to the rules document for protocol deviations. For the purpose of this analysis, significant deviations will be defined and reviewed on a case-by-case basis for each participant in a blinded data review meeting, where a significant protocol deviation is considered to be a deviation that affects primary efficacy and safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the trial. Only those protocol deviations impacting the primary endpoint will lead to exclusion from the Per Protocol Set.

4.3 PRIMARY ENDPOINT ANALYSIS

4.3.1 Definition of endpoint

The primary endpoint is the change from baseline to Week 24 in HbA1c level. For efficacy assessments of the trial, HbA1c will be measured with blood samples collected at the central laboratory at the time points specified in Section 5.7 (baseline, Week 12, Week 24). If a participant needs to receive a rescue antidiabetic therapy, the HbA1c assessment should be performed before the antidiabetic therapy is introduced. In addition, in case of study drug treatment discontinuation, participants will be followed up per protocol. In case of trial discontinuation, HbA1c assessment will be performed at the time of withdrawal. If HbA1c measurements fall out of windowed assessments (baseline, Week 12, Week 24), the results for those assessments will be excluded (considered as missing for analysis).

4.3.2 Main analytical approach

The primary estimand is the difference in the mean change from baseline to Week 24 in HbA1c level (Gla-300 vs IDeg-100) in insulin-naïve participants with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable), regardless of discontinuation of study drug treatment due to any reason or use of rescue therapies (treatment policy strategy).

The statistical hypothesis associated with the primary non-inferiority analysis of change from baseline in HbA1c level to Week 24 is:

H_0: $\mu_{Gla\text{-}300} - \mu_{IDeg\text{-}100} \geq 0.3\%$

H_1: $\mu_{Gla\text{-}300} - \mu_{IDeg\text{-}100} < 0.3\%$

where $\mu_{Gla\text{-}300}$ and $\mu_{IDeg\text{-}100}$ denote the true mean change from baseline to Week 24 in HbA1c level for Gla-300 and IDeg-100, respectively.

If the non-inferiority is demonstrated, the hypothesis for testing superiority will be:

H_0: $\mu_{Gla\text{-}300} - \mu_{IDeg\text{-}100} = 0\%$

H_1: $\mu_{Gla\text{-}300} - \mu_{IDeg\text{-}100} \neq 0\%$

HbA1c data collected after ICEs (discontinuation of study drug treatment due to any reasons, use of rescue therapies) will be included in the analysis based on the ITT set. Missing data will be handled using a MI strategy dependent on treatment-completion status:

- Missing data from participants discontinuing the study drug treatment will be imputed using data from participants also discontinuing the study drug treatment but who have their endpoint assessed within each treatment arm.

- Missing data from participants completing the 24-week treatment period will be imputed using a model estimated from data observed in other participants completing the study drug treatment within each treatment arm.

The number (%) of participants for each missing pattern will be summarized by treatment group for the ITT set:

- Patients with non-missing baseline HbA1c data but without post-baseline HbA1c data.
- Patients with non-missing baseline and Week 12 HbA1c data who are missing Week 24 HbA1c data.
- Patients with non-missing baseline and Week 24 Hba1c data who are missing Week 12 HbA1c data.

The following two-step approach will be used for the MI:

- Step 1: The Markov chain Monte Carlo (MCMC) method will be used to impute intermediate missing data to create a monotone missing data pattern.
- Step 2: Using the 100 imputed datasets with monotone missing data pattern obtained from Step 1, missing data will then be imputed for each imputed data set using the sequential regression method.

The imputation model for Step 1 will be performed by randomized treatment arm and include baseline HbA1c value and HbA1c values at Week 12 and Week 24 and use SEED=17007. Step 1 will impute intermediate missing data to a monotone missingness pattern and create 100 imputed datasets (the SAS default of 1000 burn-in iterations for MCMC will be used when creating the 100 imputed datasets). The number of imputations may be increased if large variability of the results produced with increasing number of imputations before reaching 100 imputations is observed.

The imputation model for Step 2 will include the same variables as in Step 1, as well as randomization strata: SU use (Yes, No) and eGFR at Screening (<45 mL/min/1.73 m^2; ≥mL/min/1.73 m^2). Step 2 will be performed based on the imputed datasets in Step 1 with monotone missing pattern, and the model will use SEED=70071. If there is an insufficient number of participants with complete data within a randomization stratum for establishing the imputation model, some randomization stratification factors may be removed from the imputation model by combining groups together where needed. In the case that there is an insufficient number of patients who have discontinued treatment but have data available at Week 24 in either treatment arm for establishing the model, treatment arm may also be removed from the model, and missing data for patients discontinuing the study drug treatment will be randomly sampled from the normal distribution, using observed baseline value as the mean of the distribution.

After completing Step 2, an analysis of covariance (ANCOVA) model will be performed for each imputed data set; this analysis will include baseline HbA1c value as a covariate, study drug treatment, and randomization strata (SU use (Yes, No) and eGFR (<45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2)) as fixed factors. Graphical methods will be used to check if there are major deviations from normality. The difference in mean change from baseline to Week 24 in HbA1c

values between treatment arms (Gla-300 vs IDeg-100) will be estimated based on the difference of LS means in the ANCOVA model. The estimated differences and associated standard errors (SEs) obtained across the imputed datasets will be combined via SAS PROC MIANALYZE to produce a single point estimate difference, corresponding SE, 2-sided 95% CI (Wald), and two-sided p-value for superiority, all based on Rubin's rules.

The test for non-inferiority will be performed at a 1-sided 2.5% significance level, and the non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI of the pooled difference in change from baseline to Week 24 in HbA1c values between Gla-300 and IDeg-100 treatment arms is <0.3%. Superiority will be established if the upper bound of the 2-sided 95% CI is <0%.

In addition, a box plot based of HbA1c from baseline to Week 24 (OC) will be produced.

4.3.3 Sensitivity analysis

Sensitivity analyses will be conducted for the ITT population to assess the robustness of the results obtained from the primary analysis described in Section 4.3.2.

Mixed-Effect Model with Repeated Measurements

An MMRM analysis based on OC and assuming MAR will be carried out via SAS PROC MIXED; this sensitivity analysis will include randomized study drug treatment (Gla-300, IDeg-100), visit (Week 12, Week 24), and stratification factors at randomization (SU use (Yes, No) and eGFR (<45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2) as fixed factors, continuous baseline HbA1c value as a covariate, and treatment-by-visit and baseline HbA1c value-by-visit interactions. An unstructured covariance matrix will be used to model the within-participant errors. Graphical methods will be used to check if there are major deviations from normality. Parameters will be estimated using the restricted maximum likelihood method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. In this analysis, no imputation of missing data will be performed. The difference in mean change from baseline to Week 24 in HbA1c between treatment arms (Gla-300 vs IDeg-100) will be estimated based on the baseline adjusted MMRM model. The estimates will be presented together with their corresponding SE, 95% CI and 2-sided p-value for superiority at Week 24.

Penalized MI (For Non-Inferiority Only)

Separately, penalized MI will be performed as an additional sensitivity analysis (for non-inferiority only). The multiply imputed missing HbA1c values at Week 24 in the primary analysis will be penalized by adding 0.3% (corresponding to the non-inferiority margin) to the imputed HbA1c value in the Gla-300 arm, whereas the imputed HbA1c in the IDeg-100 arm will not be penalized. Each imputed complete dataset will then be analyzed using the same ANCOVA as described for the primary analysis in Section 4.3.2. The treatment differences and their SEs estimated from each imputed (penalized or not) dataset will be combined using Rubin's rules for a point estimate and presented with associated 2-sided 95% CI (Wald).

Reference-Based MI (For Superiority Only)

Reference-based MI assuming missing not at random (MNAR) pattern of missingness will also be performed (for superiority only). The reference-based MI approach will assume that the trajectory of withdrawals from the Gla-300 arm due to any reason is the same as that in the IDeg-100 arm. Following the completion of Step 1 (impute to monotone step) as described in the primary analysis approach in Section 4.3.2, missing Week 12 HbA1c values and Week 24 HbA1c values in the Gla-300 arm will then be imputed using a sequential regression imputation model established using data in the IDeg-100 arm. Each imputed complete dataset will be analyzed using the same ANCOVA as described for the primary analysis in Section 4.3.2. The treatment differences and their SEs estimated from each imputed dataset will then be combined using Rubin's rules for a point estimate and presented with associated two-sided p-value for superiority and 2-sided 95% CI (Wald).

4.3.4 Analysis of supplementary estimand (For non-inferiority only)

An analysis will also be performed to estimate the supplementary estimand. It will be performed for the ITT population to support non-inferiority only. For this analysis, data collected after discontinuation of study drug treatment due to any reasons or after use of rescue therapies will be excluded in the analysis of change from baseline to Week 12 and Week 24 in HbA1c level (Gla-300 vs IDeg-100) (hypothetical strategy).

An MMRM based on OC and assuming MAR will be performed for the change from baseline in HbA1c values at Week 12 and Week 24, and it will include study drug treatment, visit, and stratification factors at randomization (other than categorized Hb1Ac) as fixed factors, baseline HbA1c value as a covariate and treatment-by-visit and baseline HbA1c value-by-visit interactions. Graphical methods will be used to check if there are any major deviations from normality. An unstructured covariance matrix will be used to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Least-squares means, differences, and associated SEs will be presented with 2-sided 95% CIs.

4.3.5 Supportive analysis of supplementary estimand (For non-inferiority only)

As a supportive analysis of the supplementary estimand, a per-protocol analysis based on the PPS will be performed for non-inferiority. An MMRM assuming MAR will be performed as described for the primary analysis in Section 4.3.3. Least-squares means, differences, and associated SEs will be presented with 2-sided 95% CIs. The analysis will also be repeated for the ITT set.

4.3.6 Subgroup analyses

An ANCOVA model similar to that described for the primary analysis in Section 4.3.2 will be performed for each of the following subgroups, including a treatment-by-subgroup interaction term (if the minimum number of participants in each subgroup is at least 20):

- Age (<65 years; ≥65 years)
- Baseline HbA1c (<8.5%; ≥8.5%)

- SGLT-2i use (yes; no)
- GLP-1 RA use (yes; no)
- SU use (yes; no)
- eGFR
  - <45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2
  - 15 - <30 mL/min/1.73 m^2 ; ≥30 - <45 mL/min/1.73 m^2; ≥45 - 60 mL/min/1.73 m^2

The treatment effects (Gla-300 vs IDeg-100) across the subgroups defined for each of these factors will be estimated for the change from baseline to Week 24 in HbA1c values for the ITT population. The ANCOVA model will include a treatment-by-subgroup interaction term and a subgroup term, in addition to the following covariates which are included in the model used for primary endpoint analysis: baseline HbA1c value, study drug treatment, SU use (Yes, No), and eGFR (<45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2). In the case that the subgroup factor is identical or similar to other factor(s) in the model, those factors will be excluded from the model and the subgroup factor will be used exclusively. If the ANCOVA model does not converge, randomization strata may be removed from the model.

The mean difference in change from baseline to Week 24 in HbA1c values between treatment arms (Gla-300 vs IDeg-100) will be estimated based on the least-squares (LS) means in the model for each subgroup level. The estimated treatment means differences and their SEs obtained across the imputed datasets will be combined via SAS PROC MIANALYZE to produce a single point estimate difference along with a 2-sided 95% CI (Wald) all based on Rubin's rules. In addition, the p-value of the treatment-by-subgroup interaction will be presented.

In addition to the analyses described above, a forest plot will be presented for each of the subgroup analyses listed above and will present the number, the LS means differences (SE) between treatments and their associated 2-sided 95% CIs. The p-value of the treatment-by-subgroup interaction will also be presented.

Further subgroup analyses may be performed if deemed necessary for interpretation of results.

4.4 SECONDARY ENDPOINTS ANALYSIS

4.4.1 Secondary endpoints

4.4.1.1 Definition of endpoints

- **Change from baseline to Week 24 in fasting plasma glucose (FPG):** blood samples will be collected to measure FPG levels at the central laboratory at the time points specified in Section 5.7. For scheduled site visits, participants will be required to arrive having fasted (no intake of food or drink, except water, in the 8 hours before blood sampling) without administering the study drug.

- **Change from baseline to Week 24 in fasting SMPG:** participants will be required to measure fasting SMPG values (using the glucose meter supplied during the screening period) before breakfast and before administration of the study drug once daily throughout the treatment period; results will be recorded in the participant's electronic diary (eDiary). Additional glucose measurements may be done at the investigator's discretion. Fasting SMPG measurements will be averaged for over the 7-day window preceding the date of each participant's Week 12 and Week 24 site visit and will be considered missing if there are less than 4 days of SMPG measurements in the week preceding the visit. Baseline values will not be based on a weekly average and will instead be identified as described in Section 4.1.
- **Change from baseline to Week 24, per time point within 24-hour period in 7-point SMPG profiles:** the 7-point SMPG profile will be measured using the participant's glucose meter and recorded in the eDiary at the following 7 points: pre-prandial breakfast, 2 hours after breakfast, pre-prandial lunch, 2 hours after lunch, pre-prandial dinner, 2 hours after dinner and at bedtime. Timepoints are specified in the Section 5.7. The 7-point SMPG profile will be performed over a single 24-hour period, on at least two days within the week before selected site visits. The records for each time point will be averaged for Week 12 and Week 24 measurements (including measurements taken on the 7 days preceding the visit). If less than 2 days of measurements (a 'day' being a 24-hour period including each time point) are completed for a time point, the SMPG value will be considered missing for that time point. Baseline values will not be based on a weekly average and will instead be identified as described in Section 4.1.
- **Percentage (%) of participants reaching HbA1c target of <7.0% at Week 24:** blood samples will be collected to measure HbA1c at the different time points specified in the Section 5.7. The number and percentage of subjects reaching the HbA1c target of <7.0% at Week 24 will be presented. If a participant has a missing HbA1c value at Week 24, it will be assumed that they did not reach an HbA1c target of <7.0%.

4.4.1.2 Main analytical approach

All secondary endpoints will be analyzed for the ITT set.

The continuous secondary endpoints described above will be analyzed using the same main analytical approach as described for the primary endpoint in Section 4.3.2. Missing data will be multiply imputed as described in Section 4.3.2 for the primary endpoint analysis. The imputation model for Step 1 will use the corresponding baseline continuous endpoint value as a covariate, and continuous endpoint values at Week 12 and 24 as variables; the imputation model for Step 2 will additionally include all stratification factors at randomization (categorized baseline HbA1c value ([8.5%, ≥8.5%], SU use [yes, no], and eGFR [<45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2]).

Following imputation of missing data, an ANCOVA model will be performed for each imputed data set; this analysis will include the continuous baseline secondary endpoint value as a covariate, study drug treatment, and randomization strata (categorized baseline HbA1c value [<8.5%, ≥8.5%], SU use [yes, no] and eGFR [<45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2]) as fixed factors. The difference in mean change from baseline to Week 24 in each continuous

secondary endpoint's values between treatment arms (Gla-300 vs IDeg-100) will be estimated based on the difference of LS means in each ANCOVA model. The estimated differences and associated SEs obtained across the imputed datasets will be combined via SAS PROC MIANALYZE to produce a single point estimate difference along with a 2-sided 95% CI (Wald) and nominal 2-sided p-value, all based on Rubin's rules.

Box plots based on OC will also be produced for each of the continuous endpoints from baseline to Week 24, other than the 7-point SMPG profile data, for which a line plot of mean and standard error will be plotted for each time point.

For the categorical secondary endpoint (participants reaching HbA1c target of <7.0% at Week 24), a logistic regression model with terms of treatment arm, stratification at randomization (SU) use (Yes, No), and eGFR (<45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2), and HbA1c value at baseline will be performed. If a patient has a missing HbA1c value at Week 24, the endpoint will be imputed, and it will be assumed that they did not reach an HbA1c target of <7.0%. The adjusted odds ratio (OR) estimated from the model will be presented together with a 2-sided 95% CI and nominal 2-sided p-value.

A bar chart based on OC will also be presented that displays the frequency and percent of participants reaching the HbA1c target of <7.0% at Week 24 by treatment arm.

Note that if superiority is achieved for the primary endpoint (change from baseline to Week 24 in HbA1c level), the p-values for each secondary endpoint described as 'nominal' above will be assessed for superiority. To address the issue of Type I error related to multiple testing, the Holm procedurce will be used to control the overall family-wise Type I error rate as described in Section 4.6.

4.5 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

4.5.1 Definition of endpoints

Exploratory:

CCI

[redacted]

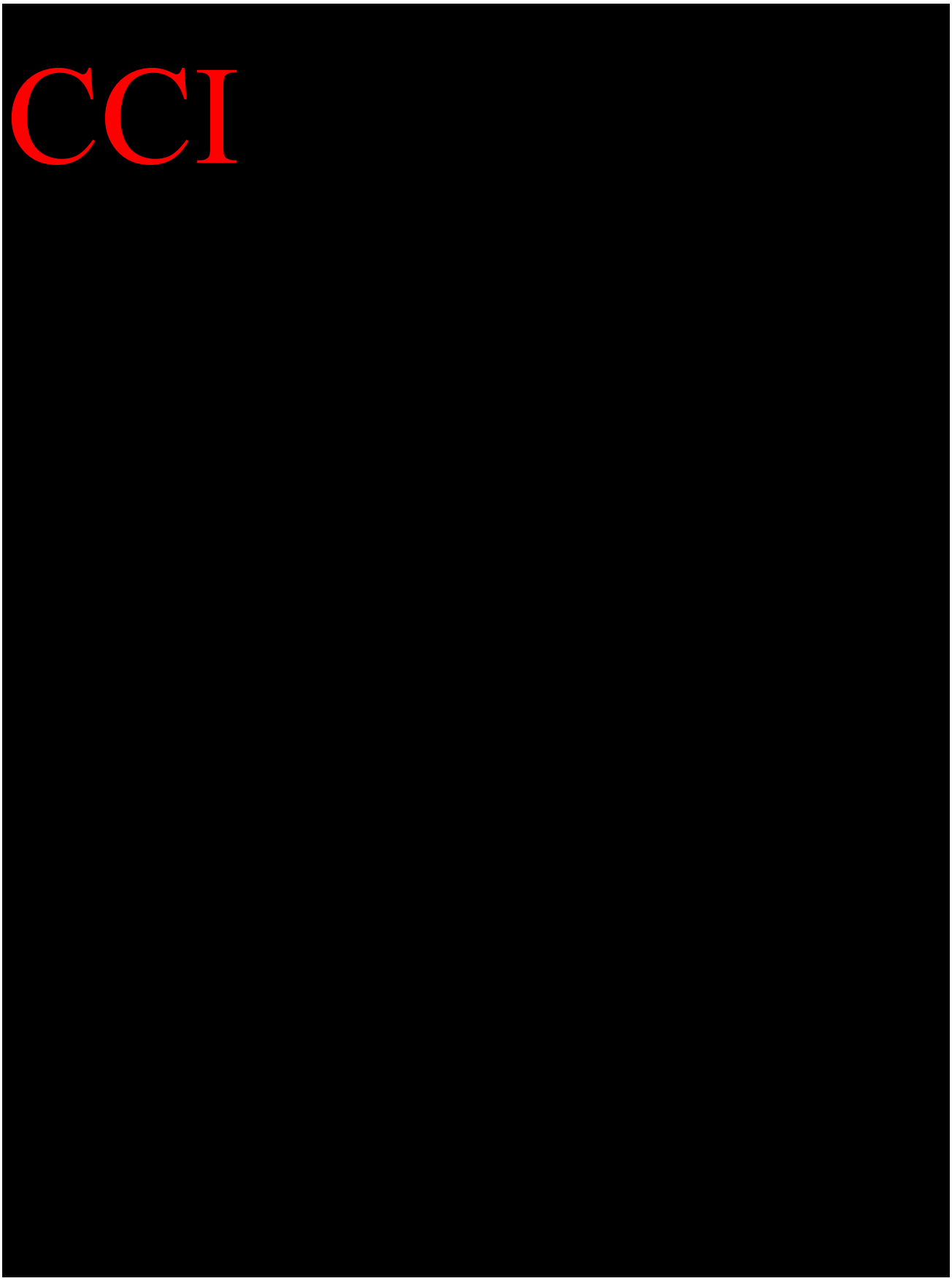
CCI

[redacted]

CCI

4.5.2 Main analytical approach

Exploratory endpoints:


CCI

4.6 MULTIPLICITY ISSUES

There is no multiplicity argument that affects switching between non-inferiority and superiority in analysis of the primary endpoint, since it corresponds to a simple closed testing procedure.

If superiority is achieved for the primary endpoint (change from baseline to Week 24 in HbA1c level), superiority will be assessed for the key secondary endpoints defined in Section 4.4.1.1. To address the issue of multiple testing, the Holm procedure will be used to control the family-wise Type I error rate:

- Let α be the significance threshold for rejecting the null hypothesis and m be the number of hypotheses.
- Order m hypotheses $(H_1, H_2, \ldots, H_m)$ by their respective p-values $(p_1, p_2, \ldots, p_m)$ from lowest to highest.
- If $p_1 < \frac{\alpha}{m}$, reject the null hypothesis; otherwise, all null hypotheses should be accepted and testing should be stopped.
- Repeat this process until $p_k < \frac{\alpha}{m+1-k}$, where k represents the first p-value that is not low enough to reject the null hypothesis H_k, at which time all remaining null hyotheses $H_1, \ldots, H_{k-1}$ are non-significant and should not be rejected.

No multiplicity adjustment will be made on the exploratory efficacy endpoints (including the CGM substudy endpoints), nor for subgroups. When presented for these analyses, 95% CIs, will be provided for descriptive purpose only.

4.7 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 3, unless otherwise specified, using the common rules:

- The analysis of the safety variables will be essentially descriptive, and no formal hypothesis testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately.

The observation period of safety data will be divided into 3 periods as defined below:

- **Pre-treatment period:** the time between the date of signed informed consent and the first injection of the open-label study drug.
- **On-treatment period:** the time from the first injection of the open-label study drug up to 7 days after the last injection of the open-label study drug, regardless of the introduction of rescue therapy. The 7-day interval is chosen based on the half-life of the study drug (approximately 5 times the half-life of IDeg-100).
- **Post-treatment period:** the time starting 8 days after the last injection of the open-label study drug.

The denominator for computation of percentages is the safety set within each treatment arm unless otherwise specified.

4.7.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure, compliance, and dose and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure (in days) is defined as last IMP administration date - first IMP administration date +1 day, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure (in weeks) is defined as (Last day of exposure - first day of exposure +1)/7. Duration of IMP exposure (in weeks) will be summarized quantitatively using descriptive statistics and categorically as below:

- ≤12 weeks
- >12 weeks to ≤24 weeks
- >24 weeks

Additionally, cumulative duration of treatment exposure expressed in participant-years will be calculated, defined as the sum of days of the duration of treatment exposure for all participants divided by 365.25.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive a once daily administration between 6:00 AM and 8:00 PM as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant will be defined as the number of injections that the participant was compliant divided by the total number of injections that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP multiplied by 100.

The number of planned injections is equal to the duration of IMP exposure (in days).

Treatment compliance will be summarized quantitatively using descriptive statistics and will also be summarized categorically: <60%, ≥60% to <80%, ≥80% to ≤100%, >100%.

Cases of overdose will constitute AESIs and will be listed as such.

Dosing

During the trial, the dose of study drug (Gla-300 or IDeg-100) will be titrated for each participant to achieve glycemic targets without hypoglycemia using a dose-adjustment algorithm. After randomization, the dose is titrated at least weekly (but no more than every 3 days) until the participant reaches a target fasting SMPG value of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. Best efforts should be made to reach the glycemic target by 8-12 weeks after randomization. Thereafter, until the end of the trial, the doses of Gla-300 and IDeg-100 will be adjusted to maintain this glycemic target, if deemed appropriate by the investigator. Dose adjustments will be based on the median value of fasting SMPG values from the last 3 measurements, including the value on the day of titration, measured by the patient using glucose meters and accessories supplied by the sponsor through a vendor.

Mean daily insulin doses received by each participant will be summarized descriptively at the end of the titration period (Week 12) and the end of the maintenance period (Week 24). The mean daily insulin dose is calculated as the mean of daily insulin doses collected over the 7 days preceding the visit. If less than 4 days of daily dosing data are available for a participant in the 7-day period preceding the timepoint, the mean daily insulin dose for that participant will be reported as missing.

The frequency and percentage of participants requiring dose adjustments after Week 12 will be presented.

A box plot of mean daily insulin dose at the end of the titration period (Week 12) and the end of the maintenance period (Week 24), will be produced, as well as a bar chart presenting the percentage (%) of participants requiring dose adjustments after Week 12.

4.7.2 Hypoglycemic events

During the trial, participants will be instructed to document any hypoglycemia events (including any possible reasons for hypoglycemia (eg, physical exercise, skipped meal)) in their eDiary. Hypoglycemia will be reported in the specific hypoglycemia event information form in the eCRF. The information recorded will include onset date and time; symptoms and/or signs; the SMPG value, if available; and the treatment, with documentation of whether the participant required outside assistance to achieve neurologic recovery. A hypoglycemia event that fulfills the seriousness criteria will also be documented on the SAE form in the eCRF.

Hypoglycemic events will be evaluated based on the following categories of interest (3, 4, 5):

- Any Hypoglycemic Event:
  - Any event recorded on the Hypoglycemic Event Information Library eCRF page that has "Yes" as the response to the question "Were any hypoglycemic events experienced", regardless of the plasma glucose measurements.
- Confirmed hypoglycemia (symptomatic, severe) - each of the events below will be captured if the response to the question "Was a glucose measurement obtained at the time of the event before countermeasure?" on the Hypoglycemic Event Information Library eCRF page is "Yes". Classification below will be dependent on glucose measurement.
  - ADA Level 1: A measurable glucose concentration of <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) that can alert a person to take action. A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a marker of physiological hypoglycemia in humans. Recurrent episodes of hypoglycemia lead to increased hypoglycemia unawareness, Therefore, glucose levels <70 mg/dL (3.9 mmol/L) are clinically important, independent of the severity of acute symptoms.
  - ADA Level 2: A measurable glucose concentration of <54 mg/dL (3.0 mmol/L) that needs immediate action. At approximately 54 mg/dL (3.0 mmol/L), neurogenic and neuroglycopenic hypoglycemia symptoms begin to occur, ultimately leading to brain dysfunction at levels <50 mg/dL (2.8 mmol/L). Neuroglycopenic symptoms, including behavioral changes, visual changes, seizure, and loss of consciousness, are the result of central nervous system neuronal glucose deprivation.
  - ADA Level 3: A severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery. Severe hypoglycemia captures events during which the symptoms associated with hypoglycemia affect a participant such that the participant requires assistance from others
- Documented Hypoglycemia (<70 mg/dL): event with a glucose level of <70 mg/dL (or <3.9 mmol/L) (with or without symptoms).
  - Documented Symptomatic Hypoglycemia: Any Documented Hypoglycemic event with a response of "Yes" to "Were symptoms present?" on the Hypoglycemic Event Information Library eCRF page will be considered a Documented Symptomatic Hypoglycemia event.

- Documented Serious Symptomatic Hypoglycemia: Any Documented Symptomatic Hypoglycemia where the participant also requires assistance from another person for recovery due to the participant's inability to help themselves (identified in the Hypoglycemic Event Information Library eCRF page as "Required Assistance Because Subject was not Capable of helping Self").
- Documented Non-Serious Symptomatic Hypoglycemia: Any Documented Symptomatic Hypoglycemia event as defined above where the participant does not require assistance from another person for recovery (identified in the Hypoglycemic Event Information Library eCRF page as "No Assistance" or "Received Assistance but Subject was Capable of Helping Self).

- Documented Asymptomatic Hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration <70 mg/dL (3.9 mmol/L). Any event with a glucose level recorded as <70 mg/dL (3.9 mmol/L) on the Hypoglycemic Event Information Library eCRF that has "No" as a response to "Were symptoms present?" will be considered an Asymptomatic Hypoglycemia event.

- Probable Symptomatic Hypoglycemia: An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but was presumably caused by a plasma glucose concentration <70 mg/dL (3.9 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose. An event will be considered a Probable Symptomatic Hypoglycemia event if the following conditions are met:
  - Response to the question "Was a glucose measurement obtained at the time of the event before countermeasure?" on the Hypoglycemic Event Information Library eCRF page is "No".
  - "Were symptoms present" is reported as "Yes" on the Hypoglycemic Event Information Library eCRF and at least one symptom is reported.
  - "Oral Carbohydrate" is marked "Yes" as a treatment of hypoglycemia on the Hypoglycemic Event Information Library eCRF page.
- Pseudo Hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level. Any event with a glucose level recorded as >70mg/dL (>3.9 mmol/L) on the Hypoglycemic Event Information Library eCRF that has "Yes" as a response to "Were symptoms present?" and at least one symptom reported will be considered a Pseudo Hypoglycemia event.
- Nocturnal Hypoglycemia: Any hypoglycemia of the above categories defined by
  - Time of the day:
    - Between 00:00 AM and 05:59 AM regardless of whether the participant was awake or woke up because of the event.
    - "Time of Event" will be reported on the Hypoglycemic Event Information Library eCRF page. An event will be considered a Nocturnal Hypoglycemia Defined by

Time of the Day event depending on whether the reported time of the event falls into the range above.

- Sleep status:
  - A Nocturnal Hypoglycemic Event Defined by Sleep Status is an event in which the participant was asleep between bedtime and before getting up in the morning and was woken up because of the event (ie, the event occurred before the morning assessment of fasting prebreakfast SMPG and before any insulin injection).
  - Any event reported as "Between Bedtime and Waking" on the Hypoglycemic Information Library eCRF page as a response to the question "When did the Hypoglycemic Event occur?", regardless of reported time of the event, will be considered Nocturnal Hypoglycemia Defined by Sleep Status).

- Daytime Hypoglycemia: Any hypoglycemia of the above categories defined by:
  - Time of the day:
    - Between 6:00 and 23:59 regardless of sleep status
    - "Time of Event" will be reported on the Hypoglycemic Event Information Library eCRF page. An event will be considered Daytime Hypoglycemia Defined by Time of the Day depending on whether the reported time of the event falls into the range above.
  - Awake status:
    - A Daytime Hypoglycemic Event Defined by Awake Status is any event that occurs while the participant was awake and before going to sleep.
    - Any event reported as "Between Waking and Bedtime" on the Hypoglycemic Information Library eCRF page as a response to the question "When did the Hypoglycemic Event occur?", regardless of reported time of the event, will be considered Daytime Hypoglycemia Defined by Awake Status.

Hypoglycemia analyses will be presented separately for the following observation periods to evaluate the potentially increased risk of hypoglycemia during the initial 12 weeks after initiating basal insulin treatment:

- Overall 24-week treatment period
- Titration period (Week 1 through Week 12)
- Maintenance period (Week 12 through Week 24)

The following hypoglycemia events will be summarized. Analysis will include both the number and percentage of participants experiencing 1 event and the total number of events, summarized using descriptive statistics:

- Any hypoglycemia events, further summarized by:
  - Observation period
  - ADA classification level

    - Diurnal distribution: 24 hour (all time), daytime, and nocturnal (0:00 to 5:59 inclusive)
- Documented Hypoglycemia, further summarized by:
    - Documented symptomatic hypoglycemia
        - Documented serious symptomatic hypoglycemia
        - Documented non-serious symptomatic hypoglycemia
    - Asymptomatic hypoglycemia
- Nocturnal Hypoglycemia Defined by Time of the Day, further summarized by:
    - ADA levels
- Nocturnal Hypoglycemia Defined by Sleep Status, further summarized by
    - ADA levels
- Daytime Hypoglycemia Defined by Time of the Day, further summarized by:
    - ADA levels
- Daytime Hypoglycemia Defined by Awake Status, further summarized by:
    - ADA levels

Bar charts will also be produced for the percentage (%) of participants experiencing at least one documented hypoglycemia event, at least one daytime hypoglycemia event (defined by sleep status), and at least one nocturnal hypoglycemia event (defined by sleep status). Each bar chart will be produced overall, and by ADA level and observation period.

ORs and corresponding 95% CIs of the Gla-300 arm compared with the IDeg-100 arm will be calculated for the overall rate of on-treatment hypoglycemic events over the 24-week period using a logistic regression model that includes treatment arm and stratification factors at randomization as fixed factors based on OC. This analysis will be repeated for each observation period and by each level of diurnal distribution and ADA level. In addition to the summary table, a forest plot will be produced for this analysis.

The overall rate of hypoglycemic events in participant-months of exposure will also be calculated and presented by treatment arm for the entire 24-week period, and then repeated for each observation period, diurnal distribution, and ADA level. The rate ratios and corresponding 95% CIs of the Gla-300 arm over the IDeg-100 arm for hypoglycemic events in patients-months of exposure will be estimated using a negative-binomial regression adjusted for stratification factors at randomization with time on treatment as an offset. In addition to the summary table, a forest plot will be produced for this analysis.

The formula for the sample hypoglycemic events rate in patients-months of exposure is:

$$\text{Hypoglycemic event rates per patient-month of exposure} = \frac{\text{Number of participants with hypoglycemic events}}{\text{Total participant-months of exposure}}$$

Total participant-months of exposure is calculated as shown below:

$$\text{Total participant-months of exposure} = \frac{12 \times (\sum_{i=1}^{n} x_i)}{365.25}$$

x_i = (last dose date for i^{th} participant − first dose date for i^{th} participant + 1)

The number as well as the rate of nocturnal hypoglycemic events (as defined by sleep status) in patient-months of exposure will also be summarized.

In addition, the distribution of the total occurrence of each episode of documented hypoglycemia will be presented by 2-hour timeframe over 24 hours during the 24-week treatment. This will be repeated for each category of documented hypoglycemia.

4.7.3 Adverse events

General common rules for adverse events (AEs)

All AEs will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) currently in use by the sponsor at the time of database lock.

The AEs will be analyzed in the following 3 categories (as defined by study periods for the safety analyses):

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened or became serious during the on-treatment period
- Post-treatment AEs: AEs that developed or worsened, or became serious during the post-treatment period

Similarly, deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 5.

Table 5 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of Pts[a, b]

a Sorting will be based on the Gla-300 group/overall incidence. In case of equal frequencies of PTs within a SOC, the alphabetic order will be applied.

b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of all TEAEs with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any treatment emergent serious adverse event (SAE)
- Any TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)
- Any TEAE leading to study discontinuation
- Any TEAE leading to permanent discontinuation of IMP
- Any treatment emergent AESI
  - Pregnancy
  - Symptomatic overdose
  - Alanine aminotransferase (ALT) increase
- Any TEAE related to local intolerability at the injection site or hypersensitivity reaction
- Any treatment-related TEAE

The AE summaries of Table 6 will be generated with number (%) of participants experiencing at least one event. A bar chart will also be produced for the percentage (%) of participants experiencing common TEAEs (≥5%) in any treatment group, presented both overall and by SOC and PT.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
Common TEAE (≥5%)	Primary SOC, HGLT, HLT and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal severity	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
TEAE leading to permanent discontinuation of IMP	Primary SOC and PT
TEAE leading to study discontinuation	Primary SOC and PT
Treatment emergent AESI	Primary SOC and PT
TEAE related to local intolerability at the injection site or hypersensitivity reaction	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Pretreatment AE	Overview[a]
	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment SAE	Overview[a]
	Primary SOC and PT

a Will include the following AE categories: any AEs, any severe AEs, any SAEs, any AEs leading to death, any AEs leading to study discontinuation, any AEs leading to permanent discontinuation of IMP, any AESIs, and any treatment-related AEs.

Analysis of deaths

In addition to the analyses of deaths included in Table 6 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods and reasons for death
- Deaths in non-randomized participants or randomized but not treated participants

Analysis of adverse events of special interest (AESIs)

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during the trial by protocol amendment. All AESIs will be reported to the Sponsor in the same timeframe as SAEs (within 24 hours).

The following AEs will be considered as AESIs in this trial:

- Pregnancy of a female participant enrolled in the trial, as well as pregnancy occurring in a female partner of a male participant enrolled in the trial with study drug/NIMP.

- Symptomatic overdose (serious or nonserious) with the study drug/NIMP.
- Increase in alanine aminotransferase (ALT; >3 × upper limit of normal [ULN])

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 7. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 5. A bar chart will also be used to present the percentage (%) of participants experiencing at least one treatment-emergent AESI, overall and by each event of interest.

Table 7 - Selections for AESIs

AESIs	Selection
Pregnancy	eCRF specific tick box on the AE page and Pregnancy All Items page
Symptomatic overdose	eCRF specific tick box on the AE page and Overdose page
ALT increase	eCRF specific tick box on the AE page

Analysis of local intolerability at the study drug injection site or hypersensitivity reactions

Any signs of local intolerability at the study drug injection site or hypersensitivity reactions should be recorded on the AE page of the eCRF. Number (%) of participants experiencing at least one event will be summarized, as well as at the primary SOC and PT level.

4.7.4 Additional safety assessments

4.7.4.1 Laboratory variables and vital signs

The following laboratory variables and vital signs variables will be analyzed from baseline to Week 24 per Section 5.7. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets: erythrocytes, platelet count, leukocytes, hemoglobin, hematocrit
- Clinical chemistry:
  - Metabolism: albumin
  - Electrolytes: sodium, potassium
  - Renal function: creatinine, eGFR, creatinine clearance. Creatinine clearance will be derived with the equation of Cockroft and Gault using weight assessed at the same visit as creatinine. The central laboratory should calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: $eGFRcr = 142 \times \min(Scr/\kappa, 1)\alpha \times \max(Scr/\kappa, 1)\text{-}1.200 \times 0.9938Age \times 1.012$ [if female](6).
  - Liver function: ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, indirect bilirubin, direct bilirubin

- Urinalysis:
  - Quantitative analysis: pH, protein, ketones, leukocytes, blood/hemoglobin, glucose
- Pregnancy test: urine or serum
- Vital signs: body weight, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) while in seated position

The tests detailed above will be performed at the central laboratory, except urine pregnancy tests, which will be performed at sites using urine pregnancy test kits that are provided by PPD. Additional tests may be performed at a local or central laboratory at any time during the trial, as deemed necessary by the investigator or required by local regulations. If a test is used to evaluate an AE (diagnostic, follow-up, outcome), the results (including the disease progression of CKD) must be entered into the CRF.

All laboratory tests with values that are considered clinically significantly abnormal during the trial should be repeated until the values return to normal/baseline or are no longer considered clinically significant by the investigator. Potentially clinically significant abnormalities (PCSA) will be flagged and the number and percentage of participants with PCSA will be presented.

Quantitative analyses

For all laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for each analysis window, as well as the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables. A scatter plot of the worst post-baseline treatment-emergent value vs baseline value will also be presented by biological function and parameter.

Analyses according to PCSA

PCSA analyses will be performed based on the PCSA list in Section 5.5. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables and vital signs variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

In addition to summary tables, the percentage (%) of participants with at least one abnormality (PCSA) during the treatment-emergent period will be presented using bar charts, by biological function and parameter.

4.7.4.2 Product complaints

All product complaint summaries during the on-treatment period (defined in Section 4.1) will be generated in the safety population and will include the number (%) of participants experiencing at least one event, the number of events and rate per participant-year.

The event rate per participant-year will be defined as the number of events divided by the cumulative duration of all participants' exposure expressed in years.

The overview of product complaints with the details below will be generated:

- Any product complaint
- Any product complaint related to AEs
- Any product complaint leading to incorrect IMP dose administration

In addition, the analyses below will be conducted.

- Any product complaint categorized by type of complaint
- AE(s) leading to product complaints by primary SOC and PT

4.8 OTHER ANALYSES

All analyses are appropriately described in other areas of the SAP.

4.9 INTERIM ANALYSES

No interim analyses are planned for this trial.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ALP:	aspartate aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BMI:	body mass index
CGM:	continuous glucose monitoring
CKD:	chronic kidney disease
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
COVID-19:	coronavirus disease 2019
CV:	coefficient of variation
DBP:	diastolic blood pressure
DTP:	direct-to-patient
EASD:	European Association for the Study of Diabetes
eCRF:	electronic case report form
eDiary:	electronic diary
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
FPG:	fasting plasma glucose
Gla-300:	insuline glargine 300 U/mL
GLP-1 RA:	glucagon-like peptide-1 receptor antagonist
GMI:	Glucose Management Indicator
HbA1c:	glycated hemoglobin
HCP:	healthcare provider
HLGT:	high-level group term
HLT:	high-level term
ICE:	intercurrent event
ICF:	informed consent form
IDeg-100:	insulin degludec 100 U/mL
IMP:	investigational medicinal product
ITT:	intent-to-treat
LLT:	lower-level term
LS:	least-squares
MAR:	missing at random
MCMC:	Markov chain Monte Carlo
MedDRA:	medical dictionary for regulatory activities
MI:	multiple imputation
MMRM:	mixed-effect model with repeated measures

MNAR:	missing not at random
NIMP:	non-investigational medicinal product
OAD:	oral antidiabetic drug
OR:	odds ratio
PCSA:	potentially clinically significant abnormality
PPS:	per protocol set
PT:	preferred term
SAE:	serious adverse event
SAP:	statistical analysis plan
SAS:	statistical analysis system
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SGLT-2i:	sodium-glucose co-transporter-2 inhibitor
SMPG:	self-measured plasma glucose
SOC:	system organ class
SoE:	schedule of events
SU:	sulfonylureas
T2DM:	type 2 diabetes mellitus
TAR:	time above range
TBR:	time below range
TEAE:	treatment-emergent adverse event
TIR:	time in range
TITR:	time in tight range
ULN:	upper limit of normal
WOCBP:	woman of childbearing potential
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

Changes to protocol-planned analyses include the following:

- Multiplicity adjustments on secondary endpoints (Section 4.1, Section 4.4.1.2, Section 4.6).
- CCI compliance rules (Section 4.5.1).
- Analysis of exploratory endpoints - CCI (Section 4.5.2).

Due to study early termination, planned analyses have been reduced in accordance with an abbreviated CSR. The list of tables, listings and figures supporting the abbreviated CSR are documented in Appendix 6 (Section 5.6) and focus on demographics, disease characteristics at baseline, exposure, participant disposition and safety. Primary and secondary efficacy data is descriptively summarized.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, MEDICAL (OR SURGICAL HISTORY), DISEASE CHARACTERISTICS AT BASELINE, PRIOR AND CONCOMITANT MEDICATIONS

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline, and prior and concomitant medications will be summarized for the ITT population. Continuous data will be summarized using descriptive statistics. Categorical data will be summarized using counts and percentages.

5.3.1 Demographics and baseline characteristics

The following demographics and baseline characteristics will be summarized for the safety and ITT populations:

- Weight (kg)
- Height (cm)
- Body mass index (BMI) in kg/m^2 as quantitative variable documented in the eCRF and in categories (<30 kg/m^2, ≥ 30 kg/m^2)
- Age in years as quantitative variable and in categories (<65 years, ≥ 65 years)
- Sex (Male, Female)
- Race (White, Black or African American, Not Reported, Unknown, Other, Multiple)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown, Other Ethnicity)
- Country (Czech Republic, Hungary, Serbia, Poland, United States)

Baseline safety and efficacy parameters (apart from those listed above) will be presented with the relevant safety and efficacy summaries.

5.3.2 Medical (or surgical) history

Medical (or surgical) history includes all relevant medical (or surgical) history during the lifetime of the participant. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Medical and surgical history will be summarized by SOC and PT for the ITT population, sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC.

5.3.3 Disease characteristics at baseline

Specific disease characteristics at baseline includes the following variables and variables related to diabetes history will be summarized for the Safety and ITT populations:

- Baseline HbA1c as quantitative variable and in categories ($<8.5\%$, $\geq 8.5\%$)

- Baseline FPG
- Baseline SMPG
- eGFR as quantitative variable and in categories (<45 mL/min/1.73 m^2; ≥45 mL/min/1.73 m^2)
- Previous use of anti-hyperglycemic therapy by medication categories (SU, Metformin, GLP-1Ras, DPPIV Inhibitors/Gliptins, SGLT2 inhibitors, TZD/Glitazones, Insulin, Other)
- Anti-hyperglycemic therapy currently taken (Yes, No)
- Age (years) at diagnosis of diabetes
- Duration of diabetes (time from diagnosis (years))
- History of gestational diabetes (Yes, No)

Continuous variables will be summarized using descriptive statistics. Categorical disease characteristic variables will be summarized using count and percentages.

5.3.4 Prior and concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first IMP administration or can be ongoing during the treatment and/or post-treatment period.
- Concomitant medications are any interventions received by the participant concomitantly to the IMP during the on-treatment period. A medication may be classified both as a prior and concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in Section 4.1)
- Post-treatment medications are those the participant continued or started during the post-treatment period (as defined in Section 4.1).
- Any technical details related to computation, dates, or imputation for missing dates are described in Section 5.4.4).

Prior, concomitant, and post-treatment medications will be summarized by anatomic and therapeutic levels defined by ATC (Anatomic Theraputic Chemical) classification for the ITT population and will be presented by treatment arm and overall.

Prior medication summaries will be sorted by decreasing frequency of anatomic class (ATC1) and therapeutic class (ATC2) based on overall incidence. In case of equal frequency (anatomic or therapeutic categories), alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. A medication may be counted in several anatomic categories.

Concomitant and post-treatment medication summaries will be sorted by decreasing frequency of anatomic class (ATC1) followed by therapeutic class (ATC2) based on incidence in the Gla-300 arm. In case of equal frequency regarding ATCs, alphabetical order will be used. Participants will be counted once in each ATC (anatomic or therapeutic categories) linked to the medication. A medication may be counted in several anatomic categories.

5.3.4.1 Non-antidiabetic medications

Prior, concomitant, and post-treatment non-antidiabetic medications will be summarized by anatomic class (ATC1) and therapeutic class (ATC2) for the ITT population and will be presented by treatment arm and overall.

Prior medication summaries will be sorted by decreasing frequency of anatomic class (ATC1) and therapeutic class (ATC2) based on overall incidence. In case of equal frequency (anatomic or therapeutic categories), alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. A medication may be counted in several anatomic categories.

Concomitant and post-treatment medication summaries will be sorted by decreasing frequency of anatomic class (ATC1) followed by therapeutic class (ATC2) based on incidence in the Gla-300 arm. In case of equal frequency regarding ATCs, alphabetical order will be used. Participants will be counted once in each ATC (anatomic or therapeutic categories) linked to the medication. A medication may be counted in several anatomic categories.

An individual listing sorted by treatment arm and subject number will be populated instead of a summary table if few non-antidiabetic medications are observed either prior or post treatment.

5.3.4.2 Antidiabetic medications

Prior, concomitant, and post-treatment antidiabetic medications will be summarized by pharmacological class (ATC3), chemical class (ATC4) and standardized medication name for the ITT population and will be presented by treatment arm and overall.

The table for antidiabetic prior medications will be sorted by decreasing frequency of pharmacological class followed by chemical class and standardized medication name based on the overall incidence across treatment arm. In case of equal frequency, alphabetical order will be used.

The tables for antidiabetic concomitant and post treatment medications will be sorted by decreasing frequency of pharmacological class followed by chemical class and standardized medication name based on the incidence in the Gla-300 treatment arm. In case of equal frequency, alphabetical order will be used.

In addition, the following specific medications will be summarized:

- Antidiabetic concomitant rescue medications will be presented by pharmacological class (ATC3), chemical class (ATC4) and standardized medication name. Table 9 below defines antidiabetic medications by pharamacological class (ATC3).

- Prohibited concomitant medications will be presented by prohibited medication category (as defined by deviation) and standardized medication name (see Table 8 below).

Table 8 - Prohibited Medications

Prohibited Medication Category	Pharmacological Class (ATC3)	Standardized Medication Name (ATC4)[a]
Insulins and analogues	A10AB, A10AC, A10AD, A10AE, A10AF	
Other blood glucose lowering drugs, excluding insulins	A10BX	Tirzepatide (ATC5: A10BX16)
Peripherally acting antiobesity products	A08AB	
Thyroid hormones	H03AA	
Corticosteroids (excluding inhaled and topical)	H02A, H02B	
Salycylic acid and derivatives	N02BA	
Ascorbic acid (Vitamin C), including combinations	A11GA, A11GB, G01AD, S01XA	Ascorbic acid (G01AD03), Ascorbic acid (S01XA15)

a Standardized medication names are provided where the prohibited medication is limited to certain medications within the provided ATC3 class.

A list of ATC3 codes to be used in identifying antidiabetic medications is shown in Table 9 below. Prior, concomitant and post-treatment antidiabetic non-insulin and rescue therapies will also be summarized per standardized drug grouping name and standardized medication name.

Table 9 - Antidiabetic Medications

Standardized Drug Grouping Name	Group ID	Pharmacological Class (ATC3)
Insulins and analogues	100	A10AB, A10AC, A10AD, A10AE, A10AF
Biguanides	101	A10BA
Sulphonamides	102	A10BC
Other blood glucose lowering drugs	103	A10BX
Other drugs used in diabetes	104	A10X
Alpha glucosidase inhibitors	105	A10BF
Thiazolidinediones	106	A10BG
Dipeptidyl peptidase-4 inhibitors	107	A10BH
Glucagon-like peptide-1 (GLP1) agonists	168	A10BJ
SGLT2 inhibitors	291	A10BK

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 Demographic formulas

Age (years) = (Year of informed consent date - Year of birth)

5.4.2 Disease characteristics formulas

Duration of diabetes (years)= (Date of informed consent - Date of diagnosis of diabetes + 1)/365.25

Age at diagnosis of diabetes (years) = Year of diagnosis of diabetes - Year of birth

5.4.3 Reference date, study day, and baseline

For efficacy analyses, the reference date is a participant's randomization date. For safety assessments, the reference date is a participant's first treatment date.

Study day is calculated as (Date of assessment - Reference date) + 1.

Baseline is the last non-missing value recorded prior to or on the reference date.

5.4.4 Missing data

For relevant categorical tabulations in demographics, baseline characteristics and compliance summaries, the number of participants with missing data are counted in a category of "Missing" but no percentages will be calculated. "Missing" category will only be presented in summaries for variables where missing data occurs. The percentages on the other rows will be based on the number of non-missing observations.

Medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior, concomitantly, or post-treatment, it will be considered as a prior, concomitant, and post-treatment medication.

Adverse events and Hypoglycemic events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment, the adverse event will be classified as treatment emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Missing date and time of first IMP administration

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after first dose day defined by the eCRF should be considered as treatment-emergent adverse events.

The exposure duration will be kept as missing.

Missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event within data collection per MedDRA PT, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

5.4.5 Analysis windows for time points

5.4.5.1 Main Study

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy and safety variables, excluding fasting SMPG (Section 4.4.1.1), SMPG 7-point profile (Section 4.4.1.1) , and basal insulin dosing data (Section 4.5.1).

All non-missing measurements (scheduled or unscheduled) will be used if the measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the assessment closest from the targeted study day will be used. If the difference is a tie between multiple assessments, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 10 - Analysis window definition

Scheduled post-baseline visit	Targeted study day	Analysis window in study days
Week 4 (Visit 6)	29	Day 2 to Day 43
Week 8 (Visit 10)	57	Day 44 to Day 71
Week 12 (Visit 14)	85	Day 72 to 127
Week 24 (Visit 17)	169	≥ Day128

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are windowed to scheduled post-baseline visits.

5.5 APPENDIX 5 CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Table 12 - Criteria for Potentially Clinically Significant Abnormalities

Parameter	PCSA
Clinical Chemistry	
ALT	By distribution analysis : >3x ULN >5x ULN >10x ULN >20x ULN
ALT and Total Bilirubin	ALT >3x ULN and TBILI >2x ULN

Parameter	PCSA
eGFR (mL/min/1.73 m^2)	<10
(Estimate of GFR based on an MDRD equation)	<15 (kidney failure)
	≥40% decrease in eGFR from baseline
	≥50% decrease in eGFR from baseline
Creatinine	≥100% change from baseline
Albumin (g/L)	Change from baseline to:
	<30
	≥30
	>300
Vital signs	
HR (bpm)	≤50 and decrease from baseline ≥20
	≥120 and increase from baseline ≥20
SBP (mmHg)	≤95 and decrease from baseline ≥20
	≥160 and increase from baseline ≥20
DBP (mmHg)	≤45 and decrease from baseline ≥10
	≥110 and increase from baseline ≥10
Weight	≥5% increase from baseline
	≥5% decrease from baseline

5.6 APPENDIX 6 TABLE OF CONTENTS FOR ABBREVIATED CSR

	Title	Analysis Set
Table		
14.1.1.1	Participant Disposition	ITT Set
14.1.1.2	Analysis Sets	Screened Set
14.1.1.3	Number of Participants Screened	Screened Set
14.1.1.4	Number of Participants Screened by Country and Site	Screened Set
14.1.2	Significant Protocol Deviations	ITT Set
14.1.3.1	Demographics and Participant Characteristics at Baseline	Safety Set
14.1.3.2	Disease Characteristics at Baseline	Safety Set
14.1.4	Medical or Surgical History at Screening by Primary SOC and PT	ITT Set
14.1.5.1	Extent of Study Treatment Exposure	Safety Set
14.1.5.2	Treatment Compliance	Safety Set
14.1.5.3	Dosing Summary	Safety Set
14.2.1.1	Baseline Summary of Primary Endpoint: HbA1c Level	ITT Set

	Title	Analysis Set
14.2.1.2	Baseline Summary of Primary Endpoint: HbA1c Level by Subgroups	ITT Set
14.2.2.	Baseline Summary of Secondary Endpoints	ITT Set
14.3.1	Overview of Adverse Event profile: Treatment-emergent Adverse Events	Safety Set
14.3.2	Number (%) of Participants with TEAE(s) by Primary SOC, HLGT, HLT and PT	Safety Set
14.3.3.	Participants with a Common TEAE (≥5%) in Any Treatment Group by Primary SOC, HLGT, HLT and PT	Safety Set
14.3.4	Number (%) of Participants with TEAE(s) Related to IMP as per Investigator's Judgment by Primary SOC and PT	Safety Set
14.3.5	Number (%) of Participants with Treatment-emergent SAEs by Primary SOC and PT	Safety Set
14.3.6	Number (%) of Participants Who Died by Study Period	Safety Set
14.3.7	Overview of Hypoglycemic Events Overall and by Observation Period, ADA Level, and Diurnal Distribution	Safety Set
Figure		
14.2.1.1	Box Plot of HbA1c Level by Analysis Visit (Observed Cases)	ITT Set
14.2.2.1	Box Plot of FPG Level by Analysis Visit (Observed Cases)	ITT Set
14.2.2.2	Box Plot of SMPG Level by Analysis Visit (Observed Cases)	ITT Set
14.2.2.3	Line Plot of 7-point SMPG Profiles, Per Time Point within 24-Hour Period by Analysis Visit (Observed Cases)	ITT Set
14.2.2.4	Bar Chart of Percentage (%) of Participants Reaching HbA1c <7.0% at Week 24 (Observed Cases)	ITT Set
Listing		
16.2.1	Participant Randomization List	ITT Set
16.2.2	Listing of Participants with at Least One Protocol Deviation	ITT Set
16.2.3.1	Listing of Participant Demographics	Safety Set
16.2.3.2	Listing of Baseline Disease Characteristics	Safety Set
16.2.5.1	Exposure to IMP	Safety Set
16.2.7.1	Listing of all AEs	Safety Set
16.2.7.2	Listing of all AEs leading to study discontinuation	Safety Set
16.2.7.3	Listing of All Participants who Died During the Study	Safety Set
16.2.7.4	Listing of On-treatment Hypoglycemic Events	Safety SEt
16.2.8	Listing of Participants with HbA1c, SMPG, or FPG values at Week 24	ITT Set

5.7 SCHEDULE OF EVENTS

5.7.1 Schedule of events for the main trial

Table 13 - Schedule of events for the main trial

Trial Period	Screening	Baseline/ Randomization	Treatment										Follow-Up
			Titration[a]						Maintenance				
Visit[b]	**1**	**2**	**3–5**	**6**	**7–9**	**10**	**11–13**	**14**	**15**	**16**	**17**[c]	**Unscheduled**[d]	**18**
Visit Type	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Phone**	**Phone**	**Clinic**	**Clinic or Phone**	**Phone**[e]
Week	**–2**	**0**	**1 to 3**	**4**	**5 to 7**	**8**	**9 to 11**	**12**	**16**	**20**	**24**		**25**
Day	**–14**	**0**	**1 to 21**	**28**	**35 to 49**	**56**	**63 to 77**	**84**	**112**	**140**	**168**		**175**
Window (Days)	**±2**	**±2**		**±3**		**±3**		**±3**	**±3**	**±3**	**±3**		**±3**
Informed consent	X												
Inclusion and exclusion criteria	X	X											
Randomization		X											
Demography (including height)	X												
Medical/Surgical history	X												
Prior/Current medications	X												
Physical examination[f]	X	X									X		
Study drug dispensing		X		X		X[g]		X				X	
SoloStar or FlexTouch pen instruction[h]		X											
Patient eDiary setup	X												
Patient eDiary completion	<----------X---------->												
Collection of eDiary		X		X				X			X	X	
Glucose meter (dispensing and instruction)	X												

Trial Period	Screening	Baseline/ Randomization	Treatment										Follow-Up
			Titration[a]						Maintenance				
Visit[b]	**1**	**2**	**3–5**	**6**	**7–9**	**10**	**11–13**	**14**	**15**	**16**	**17**[c]	**Unscheduled**[d]	**18**
Visit Type	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Phone**	**Phone**	**Clinic**	**Clinic or Phone**	**Phone**[e]
Week	**–2**	**0**	**1 to 3**	**4**	**5 to 7**	**8**	**9 to 11**	**12**	**16**	**20**	**24**		**25**
Day	**–14**	**0**	**1 to 21**	**28**	**35 to 49**	**56**	**63 to 77**	**84**	**112**	**140**	**168**		**175**
Window (Days)	**±2**	**±2**		**±3**		**±3**		**±3**	**±3**	**±3**	**±3**		**±3**
Collection of glucose meter (if mandatory by local regulation)											X		
Daily dosing of Gla-300 or IDeg-100[i]		<----------X---------->											
Study drug dose adjustments			X	X	X	X	X	X	X	X	X		
Concomitant medications		X	X	X	X	X	X	X	X	X	X		X
Study drug adherence and accountability				X				X			X		
HbA1c	X	X						X			X		
FPG[j]	X	X						X			X		
Fasting SMPG[k]		<----------X---------->											
7-point SMPG[l]		X						X			X		
Hypoglycemia events[m]	X	X	X	X	X	X	X	X	X	X	X		X
Recording of AEs and SAEs (including AESIs)	X	X	X	X	X	X	X	X	X	X	X	X	X
Product complaints		X	X	X	X	X	X	X	X	X	X	X	
Vital signs (including body weight)[n]	X	X						X			X		
Clinical chemistry[o]	X[p]										X[p]		
Hematology[o]	X												
Urinalysis[o]	X												
Spot urine albumin: creatinine ratio	X[p]										X[p]		
Pregnancy test[q]	X			X				X			X		

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; [redacted]; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cr, creatinine; DBP, diastolic blood pressure; DTP, direct-to-patient; eDiary, electronic diary; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; Gla-300, insulin glargine 300 U/mL; HbA1c, glycosylated hemoglobin; HCP, healthcare provider; IDeg-100, insulin degludec 100 U/mL; IMP, investigational medicinal product; SAE, serious adverse event; SBP, systolic blood pressure; Scr, serum creatinine; SMPG, self-measured plasma glucose; WOCBP, women of childbearing potential.

a During the titration period, the doses of Gla-300 and IDeg-100 will be adjusted using a recommended dose-adjustment algorithm. After randomization, the dose will be titrated at least weekly (but no more than every 3 days) until the patient reaches a target fasting SMPG value of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. Thereafter, until the end of the trial, the doses of Gla-300 and IDeg-100 will be adjusted to maintain this glycemic target, if deemed appropriate by the investigator. Dose adjustments will be based on a median of fasting SMPG values from the last 3 measurements, including the value on the day of titration, measured by the patient using glucose meters and accessories supplied by the sponsor through a vendor. Best efforts should be made to reach the glycemic target by 8-12 weeks after randomization.

b [redacted]

c At the end of the trial, patients should discuss with the investigator, in collaboration with their HCP, whether to continue on the Gla-300 or IDeg-100 treatment regimen or transition to an alternate antihyperglycemic therapy. All patients who withdraw from the trial prematurely will, as soon as possible, undergo all end-of-trial and follow-up assessments/procedures at a visit that should be identified as "the early trial discontinuation visit."

d An unscheduled visit can be planned anytime during the treatment period if study drug resupply is required. This will be a site visit or via phone contact with DTP-IMP delivery.
The sponsor-approved courier company will need at least 72 hours' notice to collect treatment kits from a trial site.

e This will be a phone contact, but could be a site visit if ongoing or new AEs emerge during the post-treatment period, if necessary.

f A physical examination will be performed per standard of care to assess the health status of patients. A list of assessments is provided in Section 6.2.1 of the Protocol.

g Study drug resupply at Visit 10 will be via phone contact with DTP-IMP delivery. The sponsor-approved courier company will need at least 72 hours' notice to collect treatment kits from a trial site.

h All patients will be trained by trial staff on how to use the pen correctly, how to store it, and how to change the needle to ensure that each patient is able to perform self-injection. An instruction leaflet will be provided to patients that explains how to use the disposable pen and needles. Training will be repeated during the treatment period as often as deemed necessary by site staff.

i Gla-300 or IDeg-100 should be self-administered once daily between 6:00 PM and 8:00 PM throughout the treatment period. The investigator and patient will discuss and agree upon the injection time. Gla-300 or IDeg-100 will be administered after the fasting blood sample draw during site visits. The need for dose adjustment will be assessed at each visit.

j For scheduled site visits, patients will be required to arrive having fasted without administering the study drug. Fasting is defined as no intake of food or drink, except water, in the 8 hours before blood sampling.

k Fasting SMPG values will be used to titrate and adjust study drug doses and monitor glycemic levels. Patients will be required to measure fasting SMPG values (using the glucose meter supplied during the screening period) before breakfast and before administration of study drug once daily throughout the treatment period and to record the results in the eDiary.

l The 7-point SMPG profile will be measured (and recorded in the patient's eDiary) at the following 7 points: pre-prandial and 2 hours after starting breakfast, lunch, and dinner, and at bedtime.
The 7-point SMPG profile will be performed over a single, 24-hour period, on at least 2 days within the week before selected site visits.

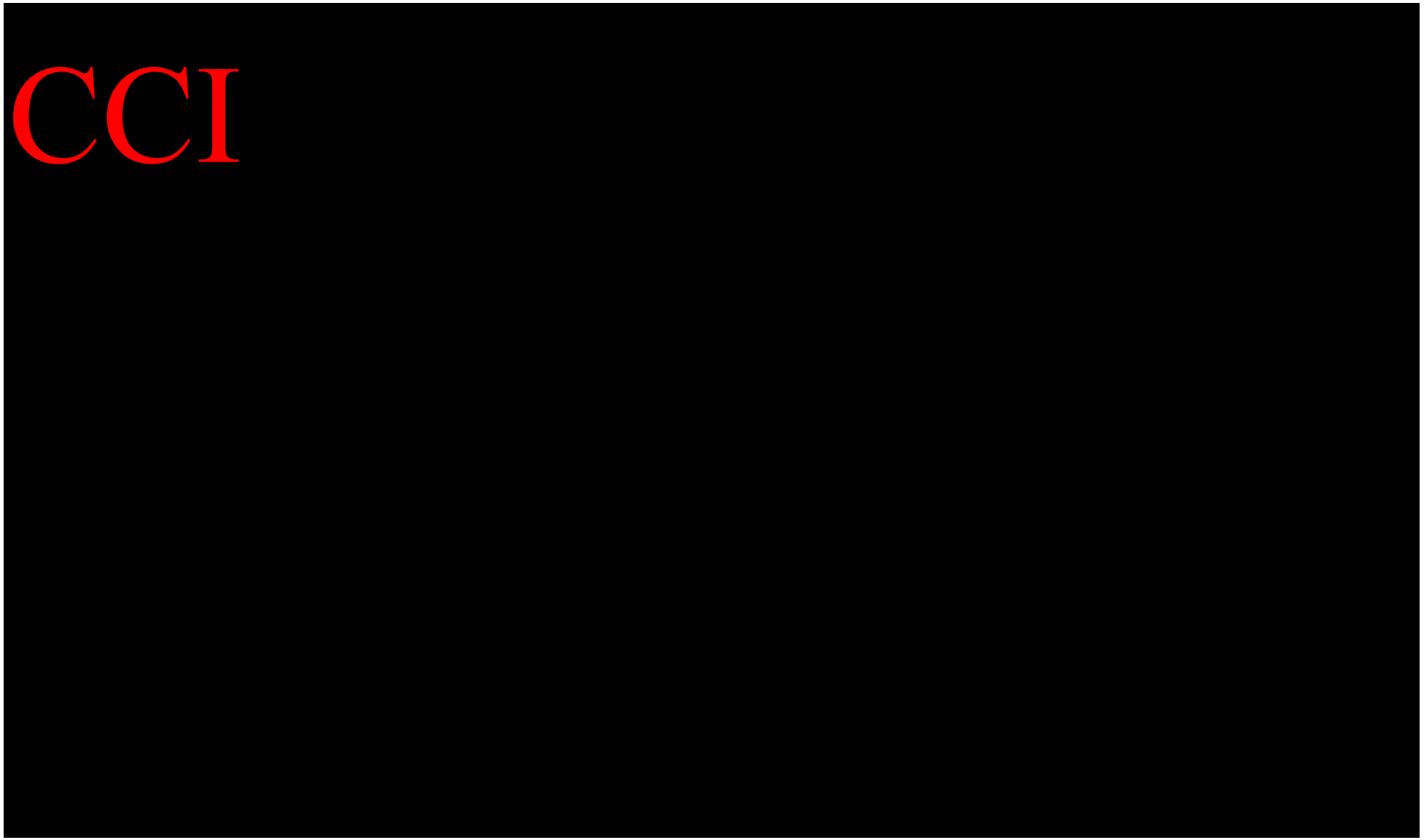
m Hypoglycemia events will be evaluated based on the categories of interest described in Section 4.7.3.

n This includes body weight, heart rate, SBP, and DBP. Height and body weight measurements at screening will be used to calculate BMI.

o The list of clinical safety laboratory tests to be performed is provided in Section 4.7.4.1. Additional tests may be performed at a local or central laboratory at any time during the trial as deemed necessary by the investigator or required by local regulations. The central laboratory should calculate eGFR using the CKD-EPI equation: $eGFRcr = 142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female] (6).

p Creatinine and eGFR (clinical chemistry) and spot urine albumin: creatinine ratio will be measured for CKD monitoring.

q This is only for WOCBP and is a urine pregnancy test.


CCI

6 REFERENCES

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lps17007-16-1-9-sap

Approve & eSign	PPD Clinical 18-Oct-2023 08:40:10 GMT+0000

Approve & eSign	PPD Clinical 18-Oct-2023 08:48:00 GMT+0000

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Sanofi**
Protocol Number:	**LPS17007**

Document Description:	Statistical Analysis Plan
SAP Title:	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
SAP Version Number:	1.0
Effective Date:	18Oct2023

Author(s):

For PPD:

PPD

Approved by:

PPD

18-Oct-2023

Date *(DD-MMM-YYYY)*

DocuSign

Certificate Of Completion

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PPD
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Status: Original
17 October 2023 | 21:30
Holder: PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17 October 2023 | 21:32 Viewed: 18 October 2023 | 09:38 Signed: 18 October 2023 | 09:42
PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	17 October 2023 | 21:32
Certified Delivered	Security Checked	18 October 2023 | 09:38
Signing Complete	Security Checked	18 October 2023 | 09:42
Completed	Security Checked	18 October 2023 | 09:42

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

PPD has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, POL-00392, Appropriate Use of Electronic Records and Electronic Signatures