CLINICAL STUDY PROTOCOL

Universal Trial Number: U1111-1272-6776

EudraCT Number: 2022-001485-35

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

LPS17007

Short Title:	Gla-300 and IDeg-100 in Insulin-Naïve People with Type 2 Diabetes Mellitus and Renal Impairment
Compound Number:	HOE901-U300 (Insulin Glargine 300 U/mL)
Trial Phase:	Phase 4
Sponsor:	Sanofi-Aventis Recherche & Développement 1 Avenue Pierre Brossolette 91380 Chilly-Mazarin Cedex, France
Sponsor Contact:	PPD
Medical Monitor:	CCI
Version of Protocol:	Original, Version 1.0
Date of Protocol:	28 Apr 2022

CONFIDENTIAL

The trial will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Trial 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
Short Title	Gla-300 and IDeg-100 in Insulin-Naïve People with Type 2 Diabetes Mellitus and Renal Impairment
Protocol Number	LPS17007
Protocol Date	28 Apr 2022

Protocol accepted and approved by:

Global Medical Lead – Toujeo

PPD

28 April 2022

Date

Declaration of Investigator

I have read and understood all sections of the protocol titled 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" and the accompanying product label.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1.0, dated 28 Apr 2022, the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Sanofi-Aventis Recherche & Développement or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients.
I agree to administer study drug only to patients under my personal supervision or the supervision of a sub-investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any trial reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Sanofi-Aventis Recherche & Développement.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	LPS17007
Universal Trial Number:	U1111-1272-6776
EudraCT Number:	2022-001485-35
Compound Number:	HOE901-U300 (insulin glargine 300 U/mL)
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
Short Title:	Gla-300 and IDeg-100 in Insulin-Naïve People with Type 2 Diabetes Mellitus and Renal Impairment
Sponsor:	Sanofi-Aventis Recherche & Développement 1 Avenue Pierre Brossolette 91380 Chilly-Mazarin Cedex, France
Trial Phase:	Phase 4
Trial Sites:	Approximate number of sites: 74
Indication:	Type 2 diabetes mellitus and renal impairment
Rationale:	Due to profoundly altered glucose and insulin metabolism, people with diabetes and chronic kidney disease (CKD) are generally at increased risk of hypoglycemia and other short- and long-term complications (Galindo et al 2020). Second-generation basal insulin analogs, such as insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL (IDeg-100), have more stable and prolonged pharmacokinetic (PK)/pharmacodynamic (PD) profiles compared with insulin glargine 100 U/mL (Gla-100; Rosenstock et al 2018; Haluzík et al 2020), a first-generation analog. The EDITION and BEGIN clinical trial programs demonstrated similar glycemic control and reduced hypoglycemia risk with Gla-300 or IDeg-100 when compared to Gla-100, with both achieving a ~1.4% decrease in glycated hemoglobin (HbA1c) in insulin-naïve people with type 2 diabetes mellitus (T2DM; Riddle et al 2014; Bolli et al 2015; Yki-Järvinen et al 2015; Roussel et al 2018; Haluzík et al 2020). Furthermore, when individual basal insulins were compared, Gla-300 mimicked the typical physiological effects on glucose and lipid

metabolism, and suppressed glucagon, with lower within-day variability than Gla-100 (Haluzík et al 2020). A subanalysis of data in insulin-naïve people with uncontrolled T2DM and renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) in the BRIGHT trial (a multicenter, open-label, parallel-group, 24-week, non-inferiority trial) showed that Gla-300 treatment resulted in significantly greater improvement in HbA1c than IDeg-100, without increasing the occurrence of hypoglycemic events (Haluzík et al 2020).

While the clinical benefits of basal insulin in people with T2DM have been documented in several clinical trials (Riddle et al 2014; Bolli et al 2015; Yki-Järvinen et al 2015; Roussel et al 2018; Rosenstock et al 2018; Haluzík et al 2020), to date there have been no dedicated randomized clinical trials comparing basal insulins in insulin-naïve people with T2DM experiencing CKD.

The TRENT trial is designed to confirm the efficacy and safety of Gla-300 compared with IDeg-100 in insulin-naïve patients with T2DM and renal impairment. It will test the hypothesis that Gla-300 is non-inferior to IDeg-100 with glucose control. If achieved, the trial will also test for the superiority of Gla-300 compared with IDeg-100 in HbA1c reduction, without an increased potential risk of hypoglycemia.

A substudy will also be conducted in the North American sites to evaluate the effects of treatment with Gla-300 compared with IDeg-100 on metrics derived from blinded continuous glucose monitoring (CGM) at Week 12 and Week 24 in patients with T2DM and renal impairment.

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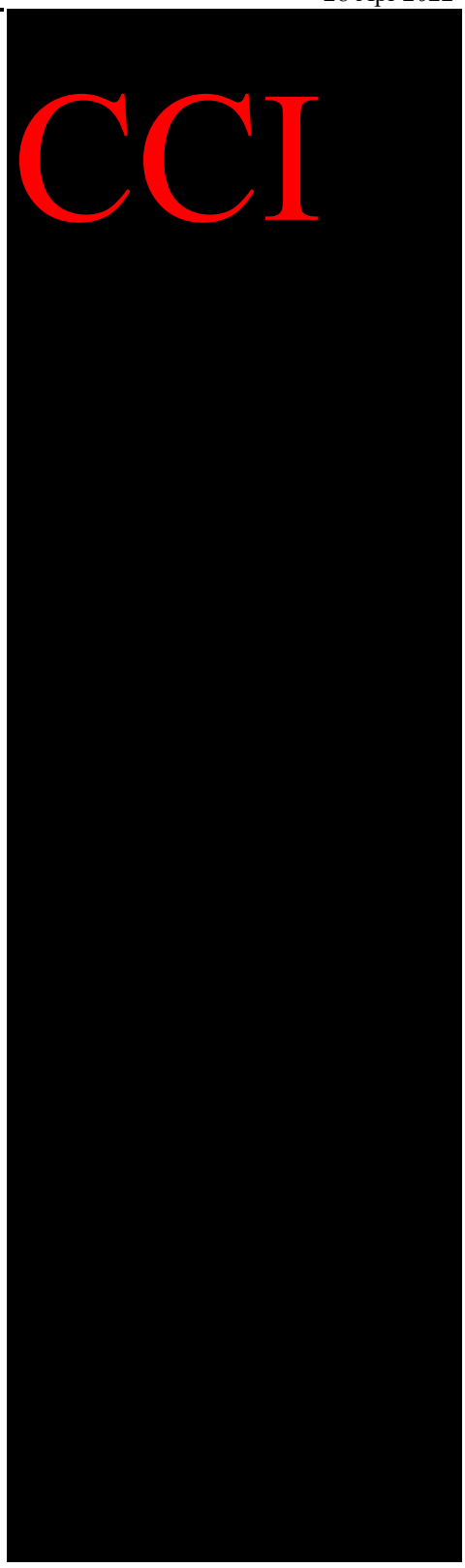
Objectives and Endpoints:

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• 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 patients with 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)	• HbA1c: Change from baseline to Week 24 (Gla-300 vs IDeg-100)
Secondary Objectives	**Secondary Endpoints**
Secondary Efficacy Objective	Secondary Efficacy Endpoints
• To evaluate the effects of treatment with Gla-300 compared with IDeg-100 on clinical parameters	• Fasting plasma glucose (FPG): Change from baseline to Week 24 • Fasting SMPG: Change from baseline to Week 24 • 7-point SMPG profiles: Change from baseline to Week 24, per time point within 24-hour period • Percentage (%) of patients reaching HbA1c target of <7.0% at Week 24
Safety Objective	Safety Endpoints
• To assess the safety and tolerability of Gla-300 and IDeg-100	• Safety evaluations of the following (during the 24-week treatment period, during the titration period, and during the maintenance period): o All hypoglycemia events (see Section 6.2.2) o The frequency of and diurnal distribution (all day, daytime, and nocturnal) of hypoglycemia by category (symptomatic, asymptomatic,

severe) per the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) hypoglycemia classification

- Local tolerability at injection site
- Hypersensitivity reactions
- Adverse events (AEs) and serious adverse events (SAEs), including adverse events of special interest (AESIs), and other safety evaluations, including vital signs and body weight

Exploratory Objectives **Exploratory Endpoints**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Patient Population:

Key Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this trial:

1. Is an adult aged ≥18 years at screening.
2. Was diagnosed with T2DM of >1-year duration and had glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable) at stable doses for ≥3 months before the screening period.
3. Has an HbA1c ≥7.5% and ≤10.5% at screening.
4. Has renal impairment, as defined by an eGFR of <60 mL/min/1.73m^2 and ≥15 mL/min/1.73m^2 (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation; National Kidney Foundation 2022).
5. Has adequately controlled blood pressure with stable antihypertensive therapy at trial inclusion.
6. Is insulin-naïve, except for short use of insulin not exceeding 15 days during the last year before the screening period.
7. Is capable of understanding the written informed consent, and provides signed written informed consent.
8. Is willing and able to complete the electronic diary (eDiary) and agrees to comply with protocol requirements.
9. Is willing and able to fast without having administered study drug for scheduled site visits. (Note: Fasting is defined as no intake of food or drink, except water, in the 8 hours before blood sampling.)

[redacted]

Key Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the trial:

1. Has initiated treatment with potential novel therapies like dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA.
2. Has a body mass index (BMI)* >45 kg/m² during the screening period.

*Body weight and height will be recorded during the screening period for the calculation of BMI (BMI = weight [kg]/[height (m)]^2).

3. Has a history of hypoglycemia unawareness (defined as the onset of neuroglycopenia before the appearance of autonomic warning symptoms [eg, blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion] or as the failure to sense a significant fall in blood glucose below normal levels).
4. Has a history of 2 or more episodes of severe hypoglycemia and/or 2 or more episodes of diabetic ketoacidosis within the 6 months before the day of screening.
5. Has been exposed to other investigational drug(s) within 1 month or
   5 half-lives from screening, whichever is longer.

[redacted]

Trial Design:

This is a multicenter, multinational, randomized, open-label, parallel-group clinical trial comparing the efficacy and safety of Gla-300 and IDeg-100 in insulin-naïve patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable), defined as an HbA1c level of ≥7.5% and ≤10.5% and an eGFR of <60 mL/min/1.73m^2 and ≥15 mL/min/1.73m^2 at screening. The trial will attempt to represent the diversity of the patient population with T2DM (eg, race, ethnicity) and renal impairment (ie, <45 mL/min/1.73m^2) through site recruitment efforts.

At the screening visit, diet and lifestyle recommendations will be provided to patients, if needed, at the investigator's discretion.

Compliance with the diet and lifestyle recommendations will be discussed with the patient throughout the trial, if needed, and more specifically if glucose levels are above target.

The trial will be conducted in approximately 630 patients. Patients will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms: Gla-300 arm or IDeg-100 arm (Figure 1).

At baseline (Day 0, Visit 2), all eligible participants will be randomly assigned to the Gla-300 arm or the IDeg-100 arm and will initiate their study drug treatment (Figure 1). They will be allowed to continue their current treatment with OADs with or without GLP-1 RA (oral or injectable; with stable doses for ≥3 months) throughout the trial period unless such treatments have to be stopped or modified for safety reasons (Section 5.2.1).

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 (Table 1). 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.

Other efficacy parameters, including HbA1c, FPG, and 7-point SMPG, will be assessed at the time points specified in the schedule of events (SoE; Table 2). Adverse events and SAEs, including AESIs, and other safety evaluations, will be assessed at the time points specified in the SoE (Table 2). Physical examination findings, hypoglycemia events, and vital signs will also be recorded to evaluate the safety of the study drug (Table 2).

The trial will consist of the following periods:

- A screening period of up to 2 weeks,
- A 24-week, open-label treatment period, including a titration period and a maintenance period.
- A 7-day, post-treatment, safety follow-up period after the last dose of the study drug or after premature/permanent discontinuation from study drug treatment. 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.

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. Discussions and final decisions made should be clearly documented in the patients' source documents.

Estimated Trial Duration:

The maximum trial duration per patient 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 patient 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).

Efficacy Assessments:

The SoE (for the main trial) is provided in Table 2. Details related to trial assessments and procedures for the CGM substudy are provided in Table 3.

The efficacy assessments are as follows:

- HbA1c measurements
- FPG measurements
- 7-point SMPG profile
- Fasting SMPG
- SMPG during symptomatic hypoglycemia

HbA1c Measurements

Blood samples will be collected to measure HbA1c at the different time points specified in the SoE (Table 2) at the central laboratory.

FPG Measurements

Blood samples will be collected to measure FPG levels at the time points specified in the SoE (Table 2) at the central laboratory. 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.

7-Point SMPG Profile

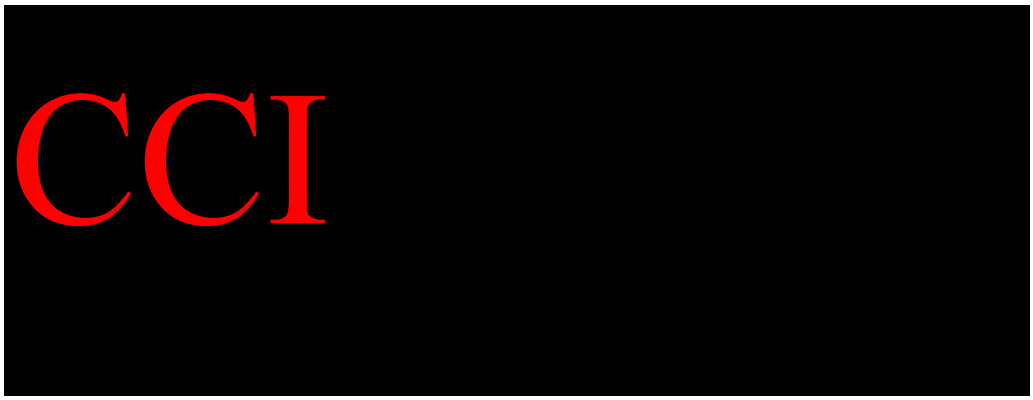
Patients will be supplied with a glucose meter and an eDiary during the screening period. Site staff will provide appropriate training to the patients on the proper use of the glucose meter and eDiary completion. The 7-point SMPG profile will be measured (and recorded in the patient's eDiary) at the following 7 points: preprandial and 2 hours after starting breakfast, lunch, and dinner, and at bedtime. The time points are specified in the SoE (Table 2).

Fasting SMPG

Fasting SMPG values will be used to titrate and adjust study drug doses and monitor glycemic levels (Table 2). Patients 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; the results will be recorded in the eDiary.

SMPG During Symptomatic Hypoglycemia

Whenever patients experience hypoglycemia symptoms, they (or others, if applicable) should measure plasma glucose (using the glucose meter supplied during the screening period), if possible. Patients will be instructed to measure plasma glucose levels before carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected (Section 6.2.2), unless safety considerations necessitate immediate carbohydrate/glucose rescue before confirmation with the SMPG values.



Safety Assessments:

The safety assessments are as follows:

- AEs and SAEs, including AESIs
- Hypoglycemia events
- Local tolerability at the injection site and hypersensitivity reactions
- Physical examination
- Vital signs
- Clinical safety laboratory assessments

Adverse Events and Serious Adverse Events, including Adverse Events of Special Interest

All AEs (serious or nonserious) will be recorded from the signing of the informed consent form (ICF) until the safety follow-up visit, the patient's permanent discontinuation from the trial, or loss to follow-up (Table 2).

The definitions of AEs and SAEs are provided in Section 13.5.
The definition of an AESI is provided in Section 6.2.6.2.

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

- Pregnancy of a female patient enrolled in the trial, as well as pregnancy occurring in a female partner of a male patient enrolled in the trial with study drug/non-investigational medicinal product (NIMP).
  - A urine pregnancy test (only for woman of childbearing potential [WOCBP]) will be performed at the time points specified in the SoE (Table 2).
  - Any female patient who becomes pregnant while participating in the trial will be discontinued from study drug treatment.

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

Hypoglycemia Events

Hypoglycemia events will be assessed at the time points specified in the SoE (Table 2).

During the trial, patients will be instructed to document any hypoglycemia events (including any possible reasons for hypoglycemia [eg, physical exercise, skipped meal]) in their eDiary. This will be reported in the specific hypoglycemia event information form in the electronic case report form (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 patient 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.

Hypoglycemia events will be evaluated based on the categories of interest listed in Section 6.2.2.

Local Tolerability at the Injection Site and Hypersensitivity Reactions

If the investigator or the patient recognizes any signs of local intolerability at the study drug injection site or hypersensitivity reactions, the event should be recorded in the AE page in the eCRF.

Physical Examination

A physical examination will be performed, per standard of care, to assess the health status of patients at the time points specified in the SoE (Table 2).

Vital Signs

Vital signs (including body weight, heart rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) will be recorded at the time points specified in the SoE (Table 2). Height and body weight measurements at screening will be used to calculate BMI.

Body Weight: Body weight will be measured to assess the change from baseline to Week 24. Self-reported weights are not acceptable.

Clinical Safety Laboratory Assessments

All clinical safety laboratory assessments (ie, hematology, clinical chemistry, urinalysis) will be performed by the central laboratory. The list of clinical safety laboratory tests to be performed is provided

in Section 13.4. The timing and frequency of sample collection are provided in the SoE (Table 2).

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, notably, the disease progression of CKD) must be entered into the eCRF.

Study Drug, Dosage, and Route of Administration:

The study drugs are Gla-300 or IDeg-100 and will be supplied as prefilled, disposable pens (Gla-300 as a SoloStar® pen and IDeg-100 as a FlexTouch® pen).

- Formulation:
  - Gla-300 will be supplied as a sterile, nonpyrogenic, clear, colorless solution in a SoloStar prefilled (disposable) pen for subcutaneous (SC) injection.
  - IDeg-100 will be supplied as a sterile, nonpyrogenic, clear, colorless solution in a FlexTouch prefilled (disposable) pen for SC injection.
- Unit dose strength(s)/Dosage level(s):
  - Gla-300: Each Gla-300 SoloStar pen contains 450 U of insulin glargine (1.5 mL of 300 U/mL insulin glargine solution).
  - IDeg-100: Each IDeg-100 FlexTouch pen contains 300 U of insulin degludec (3 mL of 100 U/mL insulin degludec solution).
- Route of administration: The study drug will be administered via SC self-injection into the abdominal area, thigh, or upper arm using the SoloStar pen or FlexTouch pen. Injection sites should be rotated within the same region from 1 injection to the next to reduce the risk of lipodystrophy.
- Time of administration: 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 at Visit 2 (baseline/randomization).

Starting Dose

Per the product label, in insulin-naïve patients with T2DM, the recommended starting dose of Gla-300 is 0.2 U/kg of body weight once daily and the recommended starting dose of IDeg-100 is 10 U once daily.

Dose Modifications

During the trial, the dose of study drug will be titrated to achieve glycemic targets without hypoglycemia using the recommended dose-adjustment algorithm (Table 1).

- 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.

Best efforts should be made to reach the glycemic target by 8-12 weeks after randomization.

Table 1 Recommended Dose-Adjustment Algorithm

Median[a] of Fasting SMPG Values From the Last 3 Measurements	Gla-300 and IDeg-100 Dose Adjustment[b]
>140 mg/dL (>7.8 mmol/L)	+6 U
>120 to ≤140 mg/dL (>6.7 to ≤7.8 mmol/L)	+4 U
>100 to ≤120 (>5.6 to ≤6.7 mmol/L)	+2 U
Glycemic target: ≥80 to ≤100 mg/dL (≥4.4 to ≤5.6 mmol/L)	No change
<80 mg/dL (<4.4 mmol/L) or occurrence of ≥1 confirmed symptomatic hypoglycemia event(s) in the preceding week	–2 U or –10% of the previous dose, or at the discretion of the investigator or any qualified designee

Abbreviations: Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; SMPG, self-measured plasma glucose.

[a] Median refers to an intermediate SMPG value (ie, the value between the lowest and the highest SMPG values when the values are ranked in a growing order).

[b] Dose adjustment should not occur more than every 3 days.

Non-Investigational Medicinal Product

The protocol-allowed background noninsulin antidiabetic drug(s) and rescue therapies used to treat hyperglycemia are considered NIMPs.

Background noninsulin antidiabetic drug(s) (ie, OADs and GLP-1 RA [oral or injectable]) that patients are receiving before screening will be continued during the treatment period unless the treatments have to be stopped or modified for safety reasons.

Rescue Therapy

"Rescue therapy," adding a new antidiabetic drug or increasing the dose of an existing antihyperglycemic, non-study drug that is part of the patient's current regimen, if needed, should be based on the investigator's decision and local labeling documents.

Statistical Methods:

Sample Size Determination

This trial is designed with a primary objective of demonstrating that Gla-300 is non-inferior to IDeg-100 regarding change from baseline to Week 24 in HbA1c level, with a non-inferiority margin of 0.3%, a 2.5% alpha risk (1-sided), and 90% power, assuming an SD of 1.1 and 10% dropouts.

A sample size of 566 randomized patients (283 per treatment arm with a 1:1 allocation ratio) is expected to ensure that the upper bound of the 2-sided 95% CI for the difference in the mean change from baseline to Week 24 in HbA1c level between Gla-300 and IDeg-100 would not exceed the non-inferiority margin of 0.3% with approximately 90% power. This calculation assumes a common SD of 1.1% with a 1-sided test at the 2.5% significant level and that the true difference in the mean change between Gla-300 and IDeg-100 is 0. Assuming a 10% dropout rate, a total of 630 patients will be randomized (315 per treatment arm).

Analysis Sets

The following analysis sets will be used in the statistical analyses:

- Safety set: The safety set will consist of all patients 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.
- Intention-to-treat (ITT) set: The ITT set will consist of all patients who sign the ICF and are randomized into the trial. All analyses using the ITT set will group patients according to randomized treatment.
- Per protocol set (PPS): The PPS will consist of all randomized patients who complete the trial without major protocol deviations.

The ITT set will be used for the primary efficacy analyses, the PPS will be used for a supportive analysis for non-inferiority, and the safety analyses will be based on the safety set. Patients' disposition will be presented for the ITT set.

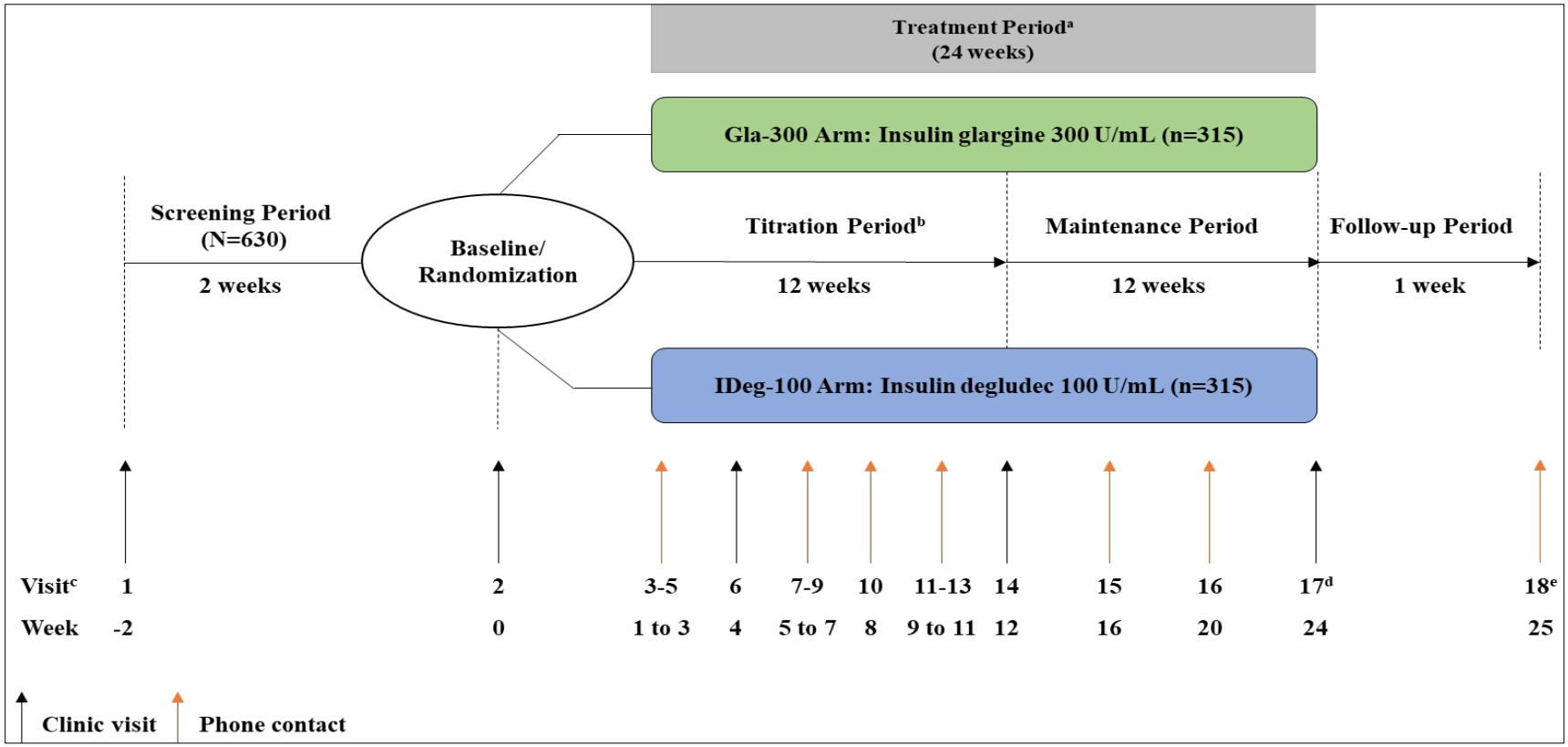
Statistical analyses will be performed using SAS software Version 9.4 or higher. Continuous variables will be summarized using the mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

All CIs presented will be 2-sided 95% CIs, unless otherwise specified. For the primary efficacy endpoint, non-inferiority will be established 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). If non-inferiority is demonstrated, superiority of Gla-300 to IDeg-100 will also be considered and established if the 95% CI lies entirely below 0%.

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model including baseline HbA1c value as a covariate, and study treatment and stratification factors at

	randomization (other than the categorized HbA1c) as fixed factors. A multiple imputation (MI) strategy will be employed for handling missing data. Safety data will be descriptively summarized using the safety set. Details of the analysis plans will be specified in a separate statistical analysis plan (SAP).
Date of Protocol:	28 Apr 2022

Figure 1 Graphical Trial Design (Main Trial)



Abbreviations: AE, adverse event; CGM, continuous glucose monitoring; DTP, direct-to-patient; Gla-300, insulin glargine 300 U/mL; HCP, healthcare provider; IDeg-100, insulin degludec 100 U/mL; IMP, investigational medicinal product; SMPG, self-measured plasma glucose.

[a] An unscheduled visit can be planned anytime during the treatment period if study drug resupply is required. This 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. 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."

[b] During the titration period, the doses of Gla-300 and IDeg-100 will be adjusted using a recommended dose-adjustment algorithm (Table 1). 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.

[c] CCI

[d] 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.

[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.

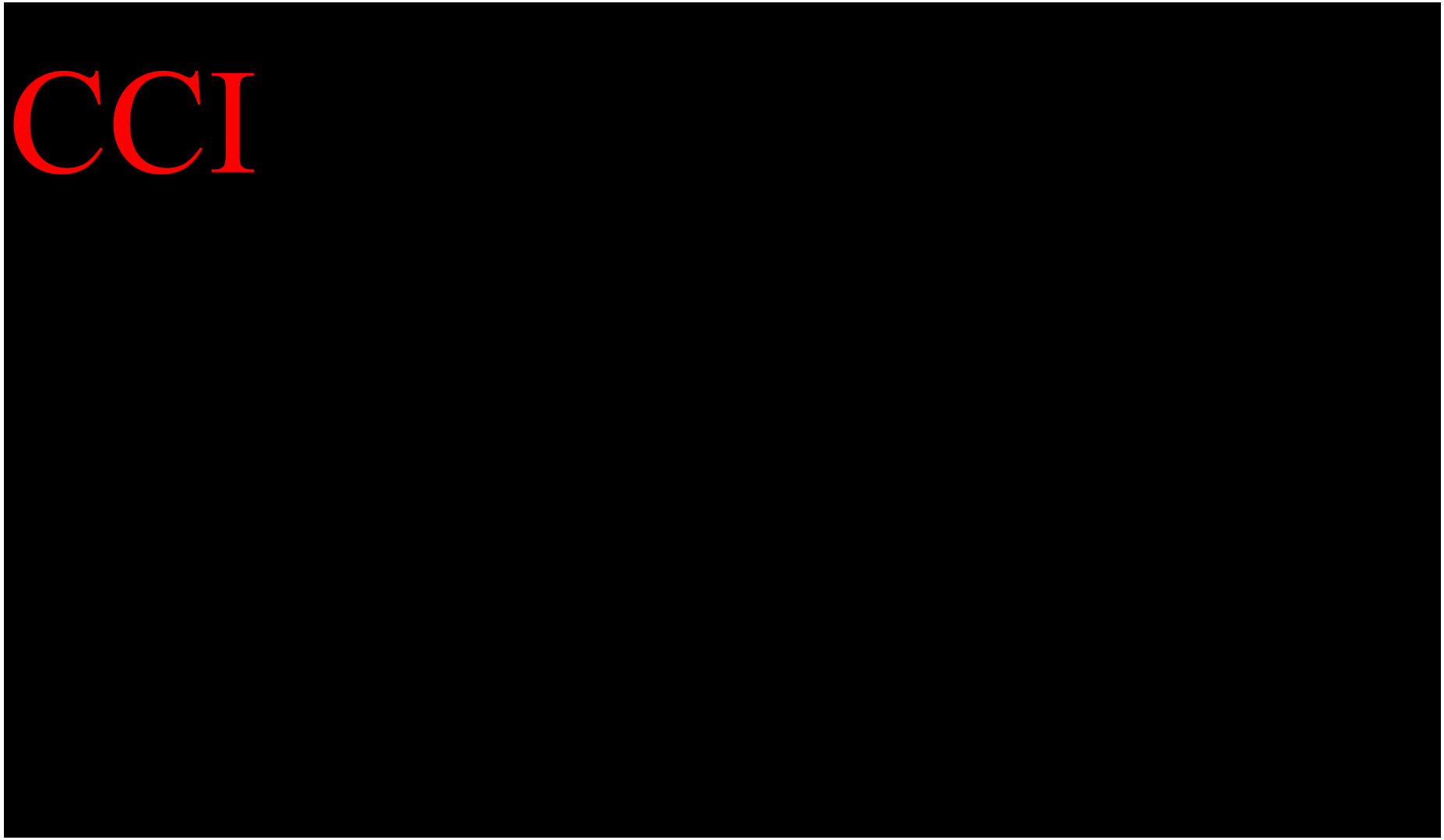

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Table 2 Schedule of Events for the Main Trial

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												
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		

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**
Concomitant medications	X	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; CGM, continuous glucose monitoring; 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 (Table 1). 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.

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[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.

[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: preprandial 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 6.2.2.

[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 13.4). 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] (National Kidney Foundation 2022).

[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.


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List of Abbreviations

Abbreviation	Definition
ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BP	blood pressure
BMI	body mass index
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNIL	Commission Nationale de l'Informatique et des Libertés
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
CVD	cardiovascular disease
DBP	diastolic blood pressure
DTP	direct-to-patient
EASD	European Association for the Study of Diabetes
eCRF	electronic case report form
EDC	electronic data collection
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation

Abbreviation	Definition
GIP	glucose-dependent insulinotropic polypeptide
Gla-100	insulin glargine 100 U/mL
Gla-300	insulin glargine 300 U/mL
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GMI	Glucose Management Indicator
HbA1c	glycated hemoglobin
HCP	healthcare provider
HLGT	high-level group term
HLT	high-level term
HRT	hormonal replacement therapy
IB	investigator's brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IDeg-100	insulin degludec 100 U/mL
IEC	independent ethics committee
IR	Investigator Registry
IRB	institutional review board
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
IWRS	interactive web response system
LAM	lactational amenorrhea method
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
NYHA	New York Heart Association

Abbreviation	Definition
OAD	oral antidiabetic drug
OR	odds ratio
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SGLT-2i	sodium-glucose co-transporter-2 inhibitor
SIP	Shared Investigator Platform
SMPG	self-measured plasma glucose
SOC	system organ class
SoE	schedule of events
SU	sulfonylureas
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAR	time above range
TBR	time below range
TEAE	treatment-emergent adverse event
TIR	time in range
ULN	upper limit of normal
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential

1 Introduction

1.1 Background Information

Chronic kidney disease (CKD) affects approximately 20% to 40% of people with diabetes and is an independent risk factor for both cardiovascular disease (CVD) and the occurrence of hypoglycemia (Rabkin 2003; Alsahli and Gerich 2014; Papademetriou et al 2015; Haluzík et al 2020). Glycemic control is vital to slowing the progression of CKD in people with type 2 diabetes mellitus (T2DM); however, lowering glycated hemoglobin (HbA1c) in severe or stage 4 CKD is not only challenging due to various patient and pharmacological factors but is also unlikely to completely arrest CKD progression (Cherney et al 2021). Hypoglycemia is a key issue for people with diabetes and CKD, as it is associated with increased morbidity and mortality, particularly in relation to CVD. Additionally, comorbid CKD increases the difficulty of managing diabetes because some treatment options, such as metformin, sulfonylureas (SUs), α-glucosidase inhibitors, and sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are contraindicated or not recommended as renal function deteriorates because of the risk of hypoglycemia, drug accumulation, or lack of glycemic efficacy (Haluzík et al 2020). Hence, there is a need for therapies that are well-tolerated and effective in lowering glucose levels in people with T2DM and CKD, which will allow them to achieve glycemic targets while minimizing hypoglycemia.

Insulin is being used increasingly to treat people with T2DM experiencing CKD, but current treatment guidelines have not provided specific guidance for insulin brand administration in this patient population (Association of British Clinical Diabetologists and The Renal Association 2021; Navaneethan et al 2021). While people with T2DM and renal impairment (early to most advanced stages of CKD) on basal and/or rapid-acting insulin continue to experience the clinical outcome benefits from optimized glycemic control, CKD puts them at increased risk of hypoglycemia compared to those with normal renal function. Moreover, because of the reduced renal insulin catabolism and impaired hypoglycemia counter-regulation in CKD, more careful titration of insulin is required in patients with reduced renal function, to minimize the risk of hypoglycemia. Therefore, it would be valuable to identify insulin options with more desirable safety profiles for people with T2DM and CKD (Haluzík et al 2020).

1.2 Rationale

Due to profoundly altered glucose and insulin metabolism, people with diabetes and CKD are generally at increased risk of hypoglycemia and other short- and long-term complications (Galindo et al 2020).

Second-generation basal insulin analogs, such as insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL (IDeg-100), have more stable and prolonged pharmacokinetic (PK)/pharmacodynamic (PD) profiles compared with insulin glargine 100 U/mL (Gla-100; Rosenstock et al 2018; Haluzík et al 2020), a first-generation analog. The EDITION and BEGIN clinical trial programs demonstrated similar glycemic control and reduced hypoglycemia risk with Gla-300 or IDeg-100 when compared to Gla-100, with both achieving a ~1.4% decrease in glycated hemoglobin (HbA1c) in insulin-naïve people with T2DM (Riddle et al 2014; Bolli et al 2015; Yki-Järvinen et al 2015; Roussel et al 2018; Haluzík et al 2020).

Furthermore, when individual basal insulins were compared, Gla-300 mimicked the typical physiological effects on glucose and lipid metabolism, and suppressed glucagon, with lower within-day variability than Gla-100 (Haluzík et al 2020). A subanalysis of data in insulin-naïve people with uncontrolled T2DM and renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) in the BRIGHT trial (a multicenter, open-label, parallel-group, 24-week, non-inferiority trial) showed that Gla-300 treatment resulted in significantly greater improvement in HbA1c than IDeg-100, without increasing the occurrence of hypoglycemic events (Haluzík et al 2020). Recent Tresiba studies have been conducted in people with T2DM who were at increased risk for hypoglycemia (Goldenberg et al 2021).

While the clinical benefits of basal insulin in people with T2DM have been well documented in several clinical trials (Riddle et al 2014; Bolli et al 2015; Yki-Järvinen et al 2015; Roussel et al 2018; Rosenstock et al 2018; Haluzík et al 2020), to date there have been no dedicated randomized clinical trials comparing basal insulins in insulin-naïve people with T2DM experiencing CKD.

The TRENT trial is designed to confirm the efficacy and safety of Gla-300 compared with IDeg-100 in insulin-naïve patients with T2DM and renal impairment. It will test the hypothesis that Gla-300 is non-inferior to IDeg-100 with glucose control. If achieved, the trial will also test for the superiority of Gla-300 compared with IDeg-100 in HbA1c

reduction, without an increased potential risk of hypoglycemia. The study will also determine if potential treatment differences can be explained based on the ease of titration of Gla-300 as well a more stable PK/PD profile compared with IDeg-100.

A substudy will also be conducted in the North American sites to evaluate the effects of treatment with Gla-300 compared with IDeg-100 on metrics derived from blinded continuous glucose monitoring (CGM) at Week 12 and Week 24 in patients with T2DM and renal impairment.

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1.3 Benefit-Risk Assessment

The safety and effectiveness of Gla-300 and IDeg-100 in people with T1DM and T2DM have been well established. Post-marketing experience with Gla-300 and IDeg-100 has demonstrated that their safety profiles are similar to those of other products in this therapeutic class. Overall, based on a review of the safety and efficacy data, the benefit-risk balance of Gla-300 and IDeg-100 under the currently approved conditions of use remains favorable; no new risks have been identified for the patient population to be included in the TRENT trial.

The starting doses of Gla-300 and IDeg-100 used in this trial are per the approved product label (ie, 0.2 U/kg body weight once daily and 10 U once daily, respectively) (TOUJEO 2020; Toujeo 300 2020; TRESIBA® 2019; Tresiba 100 2021). During the titration period of the trial, doses of Gla-300 or IDeg-100 will be titrated using the same dose-adjustment algorithm that was used in the BRIGHT trial (Rosenstock et al 2018). All eligible participants will benefit from medical care and monitoring of their glucose level. Therefore, the risk for patients participating in this trial is considered acceptable.

The important identified risks for Gla-300 and IDeg-100 are hypoglycemia or hyperglycemia associated with alterations in the insulin dosing regimen, medication errors (eg, accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting), fluid retention and heart failure (when concomitantly used with peroxisome proliferator-activated receptor-gamma agonists), and adverse reactions, such as hypoglycemia, hypersensitivity and allergic reactions, and hypokalemia (TOUJEO 2020; Toujeo 300 2020; TRESIBA® 2019; Tresiba 100 2021).

The patients with T2DM included in this trial will be insulin-naïve, will have uncontrolled glucose levels with their current therapy (as evident from an HbA1c level of ≥7.5% and ≤10.5%), and will have renal impairment (as evident from an eGFR of <60 mL/min/1.73m^2 and ≥15 mL/min/1.73m^2). Consequently, the expected improvement of glycemic control and the additional measures to improve diabetes management are considered to outweigh any potential risk associated with Gla-300 or IDeg-100 treatment.

Overall, the benefit-to-risk ratio for patients with T2DM and renal impairment who participate in this trial is considered favorable.

2 Trial Objectives, Estimands, and Endpoints

2.1 Primary Objectives, Estimands, and Endpoints

The primary objectives and estimands (including endpoints) are presented in Table 2-1.

Table 2-1 Primary Objectives, Estimands, and Endpoints

Primary Objective	Estimand Description (Including Endpoints)
• 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 patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA	• Estimand 1a (Primary): Difference in the mean change from baseline to Week 24 in HbA1c level (Gla-300 vs IDeg-100) in insulin-naïve patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA, regardless of discontinuation of study drug treatment due to any reasons and use of rescue therapies (treatment policy strategy) • Estimand 1b (Supplementary): Difference in the mean change from baseline to Week 24 in HbA1c level (Gla-300 vs IDeg-100) in insulin-naïve patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA, assuming no discontinuation of study drug treatment due to any reasons and use of rescue therapies (hypothetical strategy). This supplementary estimand will only be estimated for supporting the non-inferiority analysis

Abbreviations: Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug; T2DM, type 2 diabetes mellitus.

2.2 Secondary Efficacy Objectives and Endpoints

The secondary efficacy objectives and endpoints (including those for the [redacted]) are presented in Table 2-2.

Table 2-2 Secondary Objectives and Endpoints

Secondary Efficacy Objective	Endpoints
• To evaluate the effects of treatment with Gla-300 compared with IDeg-100 on the clinical parameters	• FPG: Change from baseline to Week 24 • Fasting SMPG: Change from baseline to Week 24 • 7-point SMPG profiles: Change from baseline to Week 24, per time point within 24-hour period • Percentage (%) of patients reaching HbA1c target of <7.0% at Week 24 •

Abbreviations: FPG, fasting plasma glucose; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; IDeg-100, insulin degludec 100 U/mL; SMPG, self-measured plasma glucose.

2.3 Safety and Exploratory Objectives and Endpoints

The safety and exploratory objectives and endpoints are presented in Table 2-3.

Table 2-3 Safety and Exploratory Objectives and Endpoints

Safety and Exploratory Objectives	Endpoints
Safety	
• To assess the safety and tolerability of Gla-300 and IDeg-100	• Safety evaluations of the following (during the 24-week treatment period, during the titration period, and during the maintenance period): o All hypoglycemia events (see Section 6.2.2). o The frequency of and diurnal distribution (all day, daytime, and nocturnal) of hypoglycemia by category (symptomatic, asymptomatic, severe) per the ADA/EASD hypoglycemia classification o Local tolerability at injection site o Hypersensitivity reactions o AEs and SAEs, including AESIs, and other safety evaluations, including vital signs and body weight

Safety and Exploratory Objectives	Endpoints
Exploratory	
[redacted]	
[redacted]	

Safety and Exploratory Objectives	Endpoints
[redacted]	

3 Investigational Plan

3.1 Trial Design

This is a multicenter, multinational, randomized, open-label, parallel-group clinical trial comparing the efficacy and safety of Gla-300 and IDeg-100 in insulin-naïve patients with 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 an HbA1c level of ≥7.5% and ≤10.5% and an eGFR of <60 mL/min/1.73m^2 and ≥15 mL/min/1.73m^2 at screening. The trial will attempt to represent the diversity of the patient population with T2DM (eg, race, ethnicity) and renal impairment (ie, <45 mL/min/1.73m^2) through site recruitment efforts.

At the screening visit, diet and lifestyle recommendations will be provided to patients, if needed, at the investigator's discretion. Compliance with the diet and lifestyle recommendations will be discussed with the patient throughout the trial, if needed, and more specifically if glucose levels are above target.

The trial will be conducted in approximately 630 patients. Patients will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms: Gla-300 arm or IDeg-100 arm (Figure 3-1).

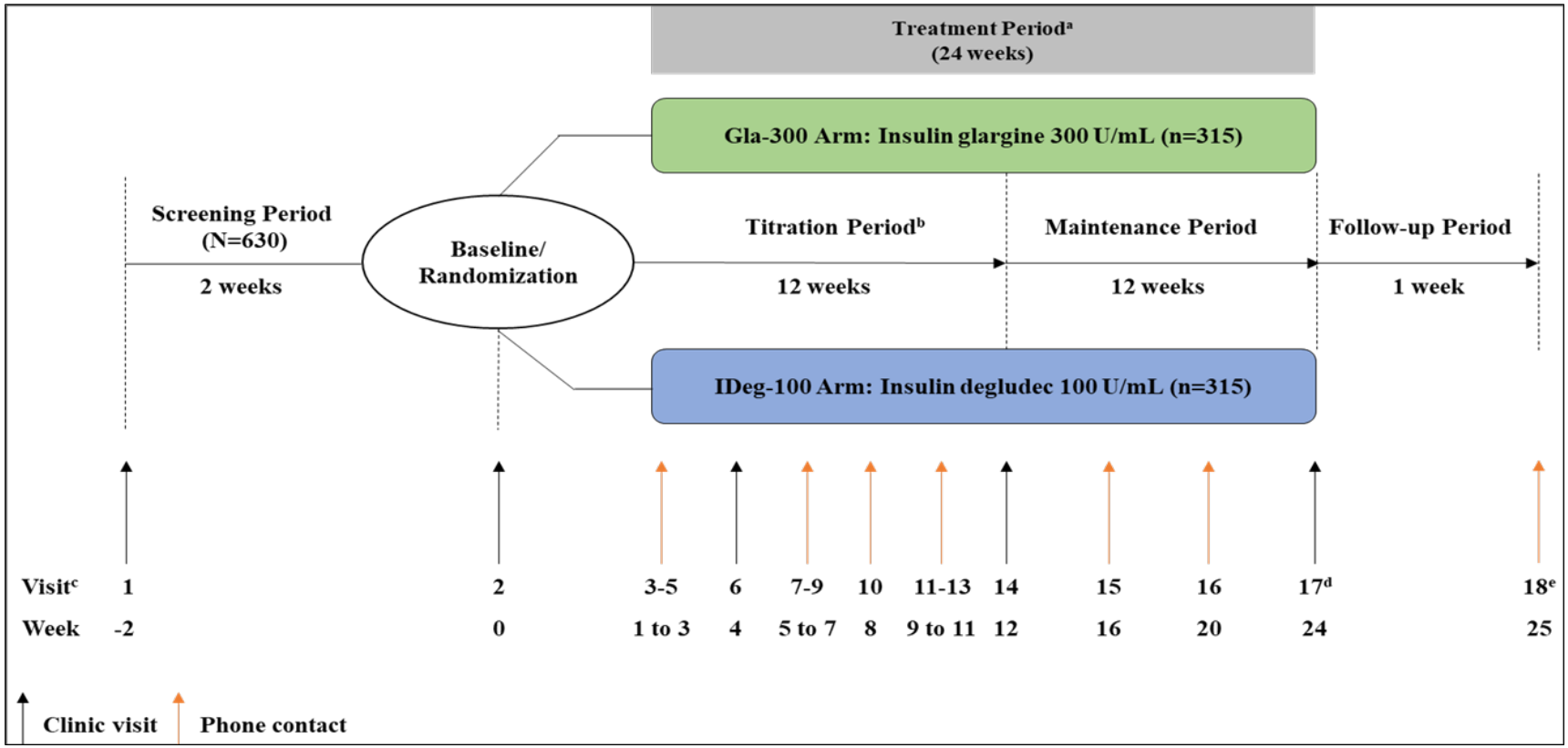
At baseline (Day 0, Visit 2), all eligible participants will be randomly assigned to the Gla-300 arm or the IDeg-100 arm and will initiate their study drug treatment (Figure 3-1). They will be allowed to continue their current treatment with OADs with or without GLP-1 RA (oral or injectable; with stable doses for ≥3 months) throughout the trial period unless such treatments have to be stopped or modified for safety reasons (Section 5.2.1).

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 (Table 5-2). 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.

Other efficacy parameters, including HbA1c, fasting plasma glucose (FPG), and 7-point SMPG, will be assessed at the time points specified in the schedule of events (SoE; Section 13.2). Adverse events (AEs) and serious adverse (SAEs), including adverse events of special interest (AESIs), and other safety evaluations will be assessed at the time points specified in the SoE (Section 13.2). Physical examination findings, hypoglycemia events, and vital signs will also be recorded to evaluate the safety of the study drug (Section 13.2).

The maximum trial duration per patient 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 patient 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).

Figure 3-1 Graphical Trial Design (Main Trial)



Abbreviations: AE, adverse event; CGM, continuous glucose monitoring; DTP, direct-to-patient; Gla-300, insulin glargine 300 U/mL; HCP, healthcare provider; IDeg-100, insulin degludec 100 U/mL; IMP, investigational medicinal product; SMPG, self-measured plasma glucose.

[a] An unscheduled visit can be planned anytime during the treatment period if study drug resupply is required. This 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. 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."

[b] During the titration period, the doses of Gla-300 and IDeg-100 will be adjusted using a recommended dose-adjustment algorithm (Table 5-2). 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.

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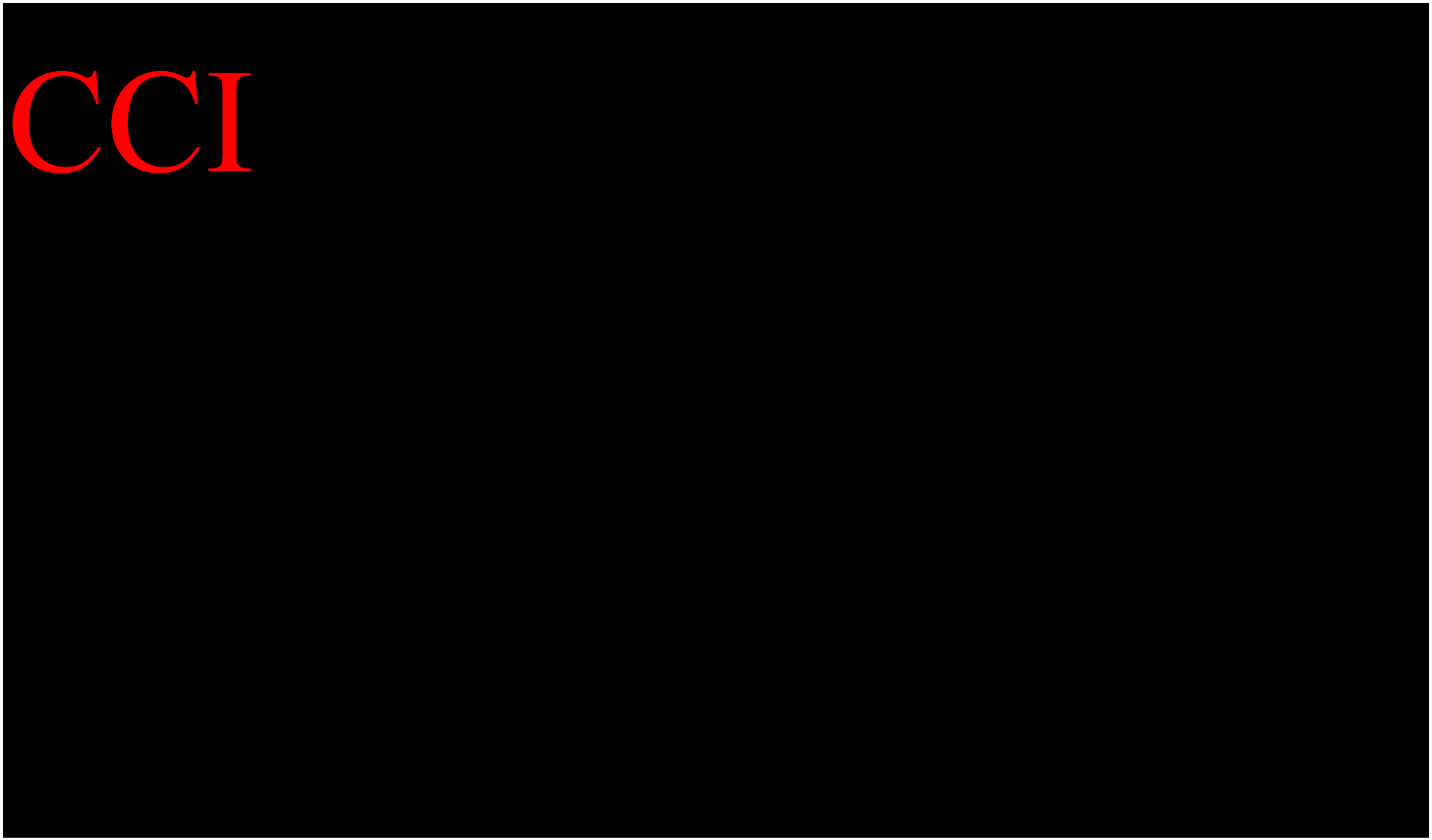
[d] At the end of the trial, patients should discuss with the investigator, in collaboration with their HCP, whether to continue on the Gla-300 or IDeg-100 treatment regimen or transition to an alternate antihyperglycemic therapy.

[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.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3.1.1 Rationale For Trial Design

This trial is designed to demonstrate non-inferiority and 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 patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable).

The design chosen for this trial (ie, randomized, open-label, parallel-group) is a classical design used to assess a causal relationship between the trial outcome and the intervention. Previously, the BRIGHT trial followed a similar treatment pattern (ie, patients were randomly assigned in a 1:1 ratio to evening dosing of Gla-300 or IDeg-100) (Rosenstock et al 2018).

As discussed in Section 1.2, although previous randomized clinical trials have demonstrated the efficacy and safety of Gla-300 and/or IDeg-100 in people with T1DM and T2DM, to date there are no dedicated prospective trials in people with T2DM and CKD. Hence, the TRENT trial is the first intended to demonstrate non-inferiority and superiority in the efficacy of Gla-300 compared with IDeg-100 in the above-mentioned patient population.

3.1.2 Duration of Trial Participation for Each Patient

The trial will consist of the following periods (further details are provided in the graphical trial design [Figure 3-1] and the SoE in Section 13.2):

- A screening period of up to 2 weeks.
- A 24-week, open-label treatment period, including a titration period and a maintenance period.
- A 7-day, post-treatment, safety follow-up period after the last dose of the study drug or after premature/permanent discontinuation from study drug treatment. 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.

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. Discussions and final decisions made should be clearly documented in the patients' source documents.

The maximum trial duration per patient will be 27 weeks. A detailed description of the assessments performed during each trial period and at each visit is provided in Section 13.2.

3.1.3 End of Trial Definition

The end of the trial is defined as the date of the last visit of the last patient in the trial globally.

A patient will be considered to have completed the trial if they completed all visits of the trial, including the safety follow-up visit, or resolution/stabilization of all SAEs and AEs with prespecified monitoring.

4 Selection of Trial Population and Discontinuation/Withdrawal

Approximately 630 patients will be enrolled at approximately 74 sites. Patients will be assigned to 1 of the 2 treatment arms only if they meet all of the inclusion criteria and none of the exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this trial:

1. Is an adult aged ≥18 years at screening.
2. Was diagnosed with T2DM of >1-year duration and had glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable) at stable doses for ≥3 months before the screening period.
3. Has an HbA1c ≥7.5% and ≤10.5% at screening.
4. Has renal impairment, as defined by an eGFR of <60 mL/min/1.73m^2 and ≥15 mL/min/1.73m^2 (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation; National Kidney Foundation 2022).
5. Has adequately controlled blood pressure with stable antihypertensive therapy at trial inclusion.
6. Is insulin-naïve, except for short use of insulin not exceeding 15 days during the last year before the screening period.
7. Is capable of understanding the written informed consent, and provides signed written informed consent.
8. Is willing and able to complete the electronic diary (eDiary) and agrees to comply with protocol requirements.

9. Is willing and able to fast without having administered study drug for scheduled site visits. (Note: Fasting is defined as no intake of food or drink, except water, in the 8 hours before blood sampling.)

10. If female, is not pregnant or breastfeeding and satisfies one of the following conditions:

    - Is a woman of nonchildbearing potential (WONCBP), as defined in the Contraceptive and Barrier Guidance section (Section 13.6).

    - Is a woman of childbearing potential (WOCBP) and agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in the Contraceptive and Barrier Guidance section (Section 13.6), during the trial treatment period (to be effective before starting the study drug treatment).

        - A WOCBP must have a negative urine pregnancy test during the screening period. (Note: If a urine test cannot be confirmed as negative [eg, an ambiguous result], a serum pregnancy test is required. In such cases, the patient must be excluded from participation if the serum pregnancy result is positive.)

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4.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the trial:

1. Has initiated treatment with new glucose-lowering medications and/or used weight loss drugs (including over-the-counter [OTC] and herbal medications), other than those stated in the inclusion criteria, within 3 months before the screening period.

2. Has initiated treatment with potential novel therapies like dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA.

3. Has a body mass index (BMI)* >45 kg/m² during the screening period.

*Body weight and height will be recorded during the screening period for the calculation of BMI (BMI = weight [kg]/[height (m)]^2).

4. Has a history of hypoglycemia unawareness (defined as the onset of neuroglycopenia before the appearance of autonomic warning symptoms [eg, blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion] or as the failure to sense a significant fall in blood glucose below normal levels).

5. Has a history of 2 or more episodes of severe hypoglycemia and/or 2 or more episodes of diabetic ketoacidosis within the 6 months before the day of screening.

6. Has been exposed to other investigational drug(s) within 1 month or 5 half-lives from screening, whichever is longer.

7. Has uncontrolled (treated/untreated) hypertension (systolic blood pressure [SBP] >180 mmHg and/or diastolic blood pressure [DBP] >95 mmHg) during the screening period.

8. Has a history of myocardial infarction, stroke, or heart failure requiring hospitalization within the 3 months before the screening period.

9. Has proliferative retinopathy or maculopathy with ongoing or anticipated requirement for active treatment prior to randomization; and/or peripheral vascular disease with ongoing or anticipated requirement for active intervention.

10. Has any of the following associated conditions/situations:

    - Conditions/concomitant diseases making them non-evaluable for the primary efficacy endpoint (eg, hemoglobinopathy or hemolytic anemia, receipt of blood or plasma products) within the 3 months before the screening period or planned to receive transfusion of blood or plasma products during the screening period.

    - Severe or unstable hepatic, gastrointestinal, cardiovascular (including congestive heart failure, according to New York Heart Association [NYHA] Functional Classification III/IV [The Criteria Committee of the New York Heart Association 1994]), respiratory, neurological, psychiatric, hematological, endocrine,

dermatological disease, active malignant tumor, other major systemic disease, or short life expectancy.

- Any disorder, except for conditions associated with T2DM, which in the investigator's opinion, might jeopardize the patient's safety or compliance with the protocol requirements.
- Acute or chronic kidney conditions with an underlying etiology, aside from diabetic nephropathy, that may require immunosuppressive treatment, or is on dialysis (eGFR of <15 mL/min/1.73m^2; verified on 2 occasions) or has planned dialysis during the screening period.
- Has a history of renal transplant.

11. Is receiving or anticipated initiation or change in concomitant medications (for >14 consecutive days) known to affect weight or glucose metabolism (eg, treatment with orlistat, thyroid hormones, or corticosteroids, excluding topical application or inhaled forms).

12. Has active liver disease or laboratory tests indicating liver damage (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 × upper limit of normal [ULN], total bilirubin >1.5 × ULN), except for documented Gilbert's syndrome, during the screening period.

13. Has nightshift working hours.

14. Is likely to require nonpermitted medications during the treatment period (Section 5.11).

15. Is currently in an institution because of a regulatory or legal order (ie, is a prisoner or a patient who is legally institutionalized).

16. Is an employee of the site or an immediate family member of the investigator or site personnel.

17. Is involved in a specific situation during trial implementation or the course of the trial that may raise ethics considerations.

18. Has hypersensitivity to any of the study drugs, or any of its excipients that, in the opinion of the investigator, contraindicates participation in the trial.

4.3 Screen Failure

Screen failures are defined as patients who provide signed written informed consent to participate in the clinical trial but are not subsequently enrolled as they do not meet all required criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information is defined as demography, screen failure reasons, eligibility criteria, and any SAEs, including AESIs.

Patients can be rescreened once before randomization in case of non-evaluable exclusion criteria or in cases where original screen failure was due to reasons expected to change at rescreening and based upon the investigator's clinical judgment. Patients can be rescreened for any other reasons or situations, if deemed necessary, at the investigator's discretion. Rescreened patients will repeat the screening visit procedures/assessments, including signing of a new informed consent form (ICF) and allocation of a new patient number.

4.4 Discontinuation From Study Drug and/or Withdrawal From the Trial

4.4.1 Discontinuation From Study Drug Treatment

All efforts should be made to keep patients on the study drug treatment. If the study drug is stopped, it should be determined whether the discontinuation can be made temporarily; permanent study drug discontinuation should be the last resort. Any study drug discontinuation should be fully documented in the electronic case report form (eCRF).

4.4.1.1 Permanent Discontinuation

In rare instances, it may be necessary for a patient to permanently discontinue the study drug.

Patients will be followed up according to the trial procedures specified in this protocol up to the scheduled date of trial completion, or up to recovery or stabilization of any AE, whichever comes last.

If possible, and after the permanent discontinuation of study drug treatment, patients will be assessed using the procedure normally planned for the last dosing day with the study drug. See the SoE (Section 13.2) for data to be collected at the time of study drug discontinuation and follow-up and for any further evaluations that need to be completed.

All cases of permanent study drug discontinuation must be recorded by the investigator in the appropriate pages of the eCRF when confirmed.

4.4.1.2 Temporary Discontinuation

Temporary study drug discontinuation decided by the investigator corresponds to more than 1 dose not administered to the patient.

Temporary study drug discontinuation may be considered by the investigator because of suspected AEs or for other reasons (eg, other medical issues). If study drug treatment is interrupted due to an AE, treatment will be reinitiated under close and appropriate clinical/and or laboratory monitoring if the investigator deems the relationship of the event to study drug as unlikely and if the trial inclusion criteria are still met.

The duration of temporary study drug discontinuation should be recorded in the appropriate eDiary pages when confirmed.

4.4.2 Lost to Follow-Up

Patients will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the site.

The following actions must be taken if a patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible. The patient should be counselled on the importance of maintaining the assigned visit schedule and asked whether they wish to and/or should continue in the trial.

- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient. The methods to contact the patient include 2 phone calls or local equivalent methods (eg, sending an email to patient's last known email address). These contact attempts should be documented in the patient's source documents.

If the patient continues to be unreachable, they will be considered to have withdrawn from the trial.

4.4.3 Handling of Withdrawals

Patients are free to withdraw from the trial at any time upon request. Their participation in the trial may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the trial, they may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Patients who permanently discontinue the study drug or active participation in the trial will no longer receive the study drug. When a patient withdraws from the trial, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF.

A patient may withdraw from the trial or study drug treatment for circumstances that include, but are not limited to, the following:

- The patient intends to become pregnant.

- The patient may be withdrawn at the discretion of the investigator due to noncompliance or due to a safety concern.

- The patient will be withdrawn if they are starting any drugs that interfere with glucose metabolism (eg, systemic glucocorticoid therapy).

- If the fasting or the mean SMPG value is >300 mg/dL, the investigator will schedule an unplanned visit as soon as possible, to obtain confirmatory FPG and investigate the cause. If no apparent or intercurrent cause is detected, the patient may be withdrawn.

- The patient has recurrent severe hypoglycemia or recurrent nocturnal hypoglycemia during the treatment period that poses a potential risk to the patient, as judged by the investigator.

- The patient needs dialysis, as judged by the investigator.

- The patient is unable to comply with the trial protocol, at the investigator's discretion.

All patients who discontinue study drug treatment will be followed up per the methods specified in this protocol. 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." Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol requirements.

Patients who withdraw from study drug treatment should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented on the relevant page of the eCRF and in the source documents.

It is vital to obtain follow-up data on any patients who withdrew because of an AE or SAE. In every case, all efforts must be made to return the patient to the site as soon as possible to perform protocol-specified, safety follow-up procedures (Section 13.2).

4.4.4 Replacements

Patients who discontinue the trial will not be replaced.

5 Trial Treatments

5.1 Study Drug

The study drugs are Gla-300 or IDeg-100 and will be supplied as prefilled, disposable pens (Gla-300 as a SoloStar® pen and IDeg-100 as a FlexTouch® pen). The details are provided in Table 5-1.

An instruction leaflet will be provided to patients that explains how to use the disposable pen and needles. All patients will be trained by site staff at Visit 2 (baseline/randomization) on how to use the pen correctly, how to store it, and how to change the needle and to ensure patients are able to self-inject (eg, set correct dose, change the needle, identify the correct injection area, complete the injection, know the appropriate storage conditions, conduct simple troubleshooting). The patient's family member or usual caregiver, if applicable, is highly encouraged to attend the training with the patient, as they play a key role and are able to support the patient with trial-related procedures during the trial. Training will be repeated during the treatment period as often as deemed necessary by site staff. These training/re-training details should be documented in the patient's source documents.

For the duration of treatment, patients will be required to use the same type of disposable pens and needles. The pen and leaflet that patients will need to use during the treatment period will be dispensed at the time points specified in the SoE (Section 13.2). Each patient will be supplied with the appropriate number of pens according to the dispensing scheme indicated in the SoE (Section 13.2).

Injection pens should never be shared with others, even if the needle is changed. Patients must always use a new needle for each injection to help ensure sterility and prevent blocked needles.

Table 5-1 Overview of Study Drug To Be Administered

Formulation	Gla-300	IDeg-100
Dosage formulation	Gla-300 will be supplied as a sterile, nonpyrogenic, clear, colorless solution in a SoloStar prefilled (disposable) pen for SC injection.	IDeg-100 will be supplied as a sterile, nonpyrogenic, clear, colorless solution in a FlexTouch prefilled (disposable) pen for SC injection.
Unit dose strength(s)/Dosage level(s)	Each Gla-300 SoloStar pen contains 450 U of insulin glargine (1.5 mL of 300 U/mL insulin glargine solution).	Each IDeg-100 FlexTouch pen contains 300 U of insulin degludec (3 mL of 100 U/mL insulin degludec solution).
Route of administration	The study drug will be administered via SC self-injection into the abdominal area, thigh, or upper arm using the SoloStar pen or FlexTouch pen. Injection sites should be rotated within the same region from 1 injection to the next to reduce the risk of lipodystrophy. (Note: The injection sites for study drug and NIMP, if taken, should be different so that any injection site reactions can be attributed specifically to the study drug or NIMP [eg, GLP-1 RA].)	

Abbreviations: Gla-300, insulin glargine 300 U/mL; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDeg-100, insulin degludec 100 U/mL; NIMP, non-investigational medicinal product; SC, subcutaneous.

5.2 Non-Investigational Medicinal Product

The protocol-allowed background noninsulin antidiabetic drug(s) (Section 5.2.1) and rescue therapies used to treat hyperglycemia (Section 5.2.2) are considered non-investigational medicinal products (NIMPs).

5.2.1 Background Noninsulin Antidiabetic Drug(s)

Background noninsulin antidiabetic drug(s) (ie, OADs and GLP-1 RA [oral or injectable]) that patients are receiving before screening will be continued during the treatment period unless the treatments have to be stopped or modified for safety reasons. Formulation and route(s) of administration of background antidiabetic therapy will be defined per local labeling.

5.2.2 Rescue Therapy

Routine fasting SMPG, central laboratory FPG measurements, and central laboratory alerts on HbA1c are set up to ensure that glycemic parameters remain under predefined threshold values. The threshold values for rescue are defined as follows:

- After Week 12 (ie, end of the titration period): FPG >200 mg/dL (11 mmol/L) and/or HbA1c >8.5%

If the patient's FPG and/or HbA1c level is above the threshold, the investigator has to ensure that no reasonable explanation exists for glycemic levels above target, and in particular that:

- Plasma glucose was actually measured in fasting condition (ie, after at least 8 hours of fasting).
- The study drug is being properly titrated according to the protocol.
- There is no intercurrent disease that may jeopardize glycemic levels (eg, infection).
- Compliance to study drug treatment, diet, and lifestyle is appropriate.

If any of the above can reasonably explain the glycemic levels being above target, the investigator should undertake appropriate action, ie,:

- Titrate basal insulin dose according to the protocol.
- Initiate an evaluation and treatment of any intercurrent disease (to be reported in AE/SAE/concomitant medication parts of the eCRF and the medical record).
- Stress the absolute need to comply with study drug treatment, and the advantages of following diet and lifestyle recommendations.
- Schedule an HbA1c and/or FPG assessment at the next visit (if the next visit is a phone call, it should be replaced by a site visit).

If none of the above reasons can be found, and/or appropriate actions fail, it is recommended that rescue therapy be initiated.

"Rescue therapy," adding a new antidiabetic drug or increasing the dose of an existing antihyperglycemic, non-study drug that is part of the patient's current regimen, if needed, should be based on the investigator's decision and local labeling documents. Adding prandial insulin may be the preferred option. The addition of a new antidiabetic drug or an increase in the dose of a background antidiabetic drug ("rescue") should not be decided based on a single FPG or HbA1c value, but rather on a thorough evaluation of the patient's glycemic levels. It is expected that the initiation of any rescue therapy will be deferred until the study drug has been optimally titrated to target (ie, Week 12 of the treatment period).

The reason for initiating rescue therapy, the type of rescue therapy, and the day of starting rescue therapy along with the dose will be documented on the appropriate pages of the eCRF.

Note: Short-term (ie, 10 consecutive days) uses of short- or rapid-acting insulin therapy (eg, due to acute illness or surgery) will not be considered as rescue therapy. All such uses of short- or rapid-acting insulin therapy must be reported in the eCRF and patient record.

All assessments for the primary and secondary efficacy and safety parameters planned at the end of the treatment period (Week 24; Section 13.2) should be performed before initiating the rescue therapy. The patient will remain in the trial and continue to administer the study drug (including background antidiabetic therapy). The planned visits and assessments should be performed until the last scheduled visit.

5.3 Storage and Dispensing

Investigators or other authorized persons (eg, pharmacists, study drug managers) are responsible for storing the study drug in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures. Control of study drug storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the compounds should be managed according to the rules provided by the sponsor.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received, and any discrepancies must be reported and resolved before use of the study drug.

The expiry date is presented on the study drug labels, and storage conditions are written on the study drug labels and in the instruction leaflet. Patients are responsible for the correct storage of “unused” and “in-use” pens after being dispensed at the site.

5.4 Method of Assigning Patients to Treatment Arms

Global Clinical Supply Manager from PPD, a clinical research organization contracted by the sponsor, will provide the treatment kit number list, and the biostatistician assigned to the trial will provide the randomization scheme to the interactive voice response system (IVRS)/interactive web response system (IWRS). Then, the IVRS/IWRS will generate the patient randomization list according to which the patients are allocated to the treatment arms.

The study drugs will be provided in open-label boxes, and each type of kit will be identified with a treatment number.

At the screening visit, the investigator or designee will contact the IVRS/IWRS center to receive the patient number. The patient number will be composed of a 12-digit number containing the 3-digit country code, the 4-digit center code, and the 5-digit patient chronological number (which is 00001 for the first patient screened in a center, 00002 for the second patient screened in the same center, etc.).

Patients will be randomized to receive Gla-300 or IDeg-100 during the 24-week comparative efficacy and safety period. The randomization ratio will be 1:1, and randomization will be stratified by HbA1c value at screening (<8.5%, ≥8.5%), SU use (Yes, No), and eGFR (<45 mL/min/1.73m^2, ≥45 mL/min/1.73m^2).

The treatment kits will be allocated using a centralized treatment allocation system (IVRS/IWRS). At Visit 2, after assessment results are reviewed and baseline assessments are completed, the IVRS/IWRS center will be contacted by the investigator or designee for randomization and the first treatment kit(s) allocation. The investigator or designee will have to call the IVRS/IWRS center to provide some information (such as patient number provided by IVRS/IWRS at screening visit, date of birth, etc.). The IVRS/IWRS will be contacted again each time new treatment kit(s) allocation is necessary (Section 13.2). The IVRS/IWRS will allocate treatment kit(s) using their treatment number.

A randomized patient is defined as a patient who is registered and assigned with a randomized treatment arm from the IVRS/IWRS, as documented from IVRS/IWRS log file regardless of whether the treatment kit was used or not.

A patient cannot be randomized more than once.

5.5 Treatments Administered

The following treatments will be administered in the trial:

- Gla-300 arm: Insulin glargine 300 U/mL
- IDeg-100 arm: Insulin degludec 100 U/mL
- Time of administration:
    - 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 at Visit 2 (baseline/randomization).
    - The first dose of Gla-300 or IDeg-100 will be administered on the evening of Day 0 (Visit 2).

Starting Dose

Per the product label, in insulin-naïve patients with T2DM, the recommended starting dose of Gla-300 0.2 U/kg of body weight once daily and the recommended starting dose of IDeg-100 is 10 U once daily.

5.5.1 Dose Modifications

During the trial, the dose of study drug will be titrated to achieve glycemic targets without hypoglycemia using the recommended dose-adjustment algorithm (Table 5-2).

- 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.

Table 5-2 Recommended Dose-Adjustment Algorithm

Median[a] of Fasting SMPG Values From the Last 3 Measurements	Gla-300 and IDeg-100 Dose Adjustment[b]
>140 mg/dL (>7.8 mmol/L)	+6 U
>120 to ≤140 mg/dL (>6.7 to ≤7.8 mmol/L)	+4 U
>100 to ≤120 (>5.6 to ≤6.7 mmol/L)	+2 U
Glycemic target: ≥80 to ≤100 mg/dL (≥4.4 to ≤5.6 mmol/L)	No change
<80 mg/dL (<4.4 mmol/L) or occurrence of ≥1 confirmed symptomatic hypoglycemia event(s) in the preceding week	–2 U or –10% of the previous dose or at the discretion of the investigator or any qualified designee

Abbreviations: Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; SMPG, self-measured plasma glucose.

[a] Median refers to an intermediate SMPG value (ie, the value between the lowest and the highest SMPG values when the values are ranked in a growing order).

[b] Dose adjustment should not occur more than every 3 days.

Sound clinical judgment is to be exercised during titration, and investigators may adjust or stop titration, or temporarily reduce the dose if they believe that further titration would result in patients experiencing any AEs (eg, hypoglycemia, AESIs).

Patients will be educated about the titration schedule so that they can monitor it with the assistance of the investigator or medically qualified designee. All discussions must be properly documented in the patient's record. If needed, additional contacts will be made available for patients to discuss dose adjustments in between the scheduled visits. It is at the discretion of the investigator to allow well-trained patients to make study drug dose adjustments in between scheduled visits without prior consultation of the site personnel.

Data relevant for study drug titration (eg, fasting SMPG, daily insulin dose, hypoglycemia occurrence) will be regularly reviewed by dedicated, qualified persons to identify patients whose basal insulin dose was not titrated according to the recommended dose-adjustment algorithm. If needed, site staff (including the investigator) can be retrained on titration procedures. The details on insulin titration monitoring will be provided in separate documents.

5.6 Identity of Study Drug

Gla-300 and IDeg-100 are sterile, nonpyrogenic, clear, colorless solutions provided in SoloStar and FlexTouch prefilled (disposable) pens, respectively, for subcutaneous (SC) injection.

Adequate supplies of the Gla-300 and IDeg-100 treatment kits to the sites will be made by PPD through appropriate channels.

The following drug supplies will be used in the trial:

Product	Supplied As
Gla-300	SoloStar pen (containing 450 U of insulin glargine [1.5 mL of 300 U/mL insulin glargine solution])
IDeg-100	FlexTouch pen (containing 300 U of insulin degludec [3 mL of 100 U/mL insulin degludec solution])

Abbreviations: Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL.

5.7 Management of Clinical Supplies

5.7.1 Study Drug Packaging and Storage

Gla-300 is a sterile, nonpyrogenic, clear, colorless solution in a 1.5 mL SoloStar prefilled (disposable), single-patient-use pen injector and is supplied by PPD. Gla-300 SoloStar pens will be supplied as open-label treatment kits containing 5 pens.

IDeg-100 is a sterile, nonpyrogenic, clear, colorless solution in a 3 mL FlexTouch prefilled (disposable), single-patient-use pen injector and is supplied by PPD. IDeg-100 FlexTouch pens will be supplied as open-label treatment kits containing 5 pens.

Packaging will be in accordance with the administration schedule. The content of the labeling will be in accordance with the local regulatory specifications and requirements.
The appropriate number of treatment kits (including pen needles as ancillary supplies) will be dispensed to provide patients with study drug coverage up to the next site visit or phone contact with direct-to-patient (DTP) study drug delivery (Section 13.2). Storage conditions and use-by end date (ie, expiry date) are part of the Gla-300 and IDeg-100 label text.

Treatment labels will indicate the treatment number used for treatment allocation.
The investigator's name, patient number, visit number, and box number will be entered manually by the site staff on the treatment box label before dispensing.

5.7.2 Study Drug Accountability

The investigator or other personnel designated by the investigator will maintain accurate records of receipt of study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the trial. The investigator or other personnel designated by the investigator will also be responsible for controlling the site stocks of the study drug and requesting any resupply, if required. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the trial, to satisfy regulatory requirements regarding drug accountability, all remaining study drug will be reconciled and retained or destroyed according to applicable regulations.

All treatment kits will be dispensed with the investigator's oversight. The investigator is also responsible for ensuring that accurate records are maintained of treatment kits being issued and returned.

Any quality issue noticed with the receipt or use of study drug (deficiency in condition, appearance, documentation, labeling, expiration date, etc.) must be promptly reported to the sponsor. Some deficiencies may be recorded through a complaint procedure (Section 6.2.8).

A potential defect in the quality of the study drug may prompt initiation of a recall procedure by the sponsor. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor, in order to recall the study drug and eliminate potential hazards.

Further details regarding product complaint management will be provided in a study-specific pharmacy manual.

Under no circumstances will the investigator supply the study drug to a third party, allow the study drug to be used other than as directed by this clinical trial protocol, or dispose of the study drug.

5.7.3 Other Supplies

5.7.3.1 Blood Glucose Meter Kit

Each patient will be provided with a blood glucose meter kit, in order to perform SMPG assessments. Site staff will provide appropriate training to the patients related to proper use of the glucose meter. The blood glucose meter kit will include a blood glucose meter, a lancing device, test strips, sterile lancets, a storage box, a control solution, and instructions for use.

The training will be repeated as often as necessary at the site visits and documented in the patient's source documents. Patients will be instructed to bring their glucose meters with them to each site visit.

The glucose meters should be calibrated according to the instructions for use, and the site should also check the glucose meters regularly using the provided control solutions for data validity.

The SMPG values stored in the glucose meter memory will be downloaded, printed out, dated, signed, and filed into the patient file. If the patient has more than one SMPG reading at the same time point, the investigator or site staff should work with the patient to identify the appropriate value to be recorded in the patient eDiary and in the eCRF. This information will help the investigator to assess treatment effects, adjust insulin doses, and assess compliance.

Note: The SMPG values to be entered in the eCRF must be checked for consistency with the information from the glucose meter. If there is inconsistency, the reason for this has to be documented. If needed, the resulting action (eg, training of the patient on correct documentation of the values) will also be documented. The confirmed values will be entered in the eCRF based on the glucose meter output values.

5.8 Overdose Management

An overdose (accidental or intentional) with the study drug/NIMP is an event suspected by the investigator or spontaneously reported by the patient. This is defined as any dose administration that, in the investigator's opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin or is at least twice the intended dose within the intended therapeutic interval.

Any overdose, with or without associated AEs, must be promptly reported in the eCRFs by the sites, who will then notify the sponsor's representative (ie, PPD Pharmacovigilance). Overdoses without signs or symptoms should be recorded as a standard overdose; any AEs associated with the overdose should be reported on the relevant AE/SAE sections in the eCRF.

5.8.1 Treatment of Overdose

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or physical activity (eg, exercise) level may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with

intramuscular/SC glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

5.9 Blinding

As Gla-300 and the control drug, IDeg-100 are distinguishable, this trial is an open-label design, and no attempt will be made to blind administration.

5.9.1 Compensation for Lack of Blinding

Despite the open-label administration of the study drug, assessment of outcomes will be based on objectively collected data, which are assessments for the efficacy variable (HbA1c, FPG) by a central laboratory blinded to treatment arms.

As Gla-300 and IDeg-100, the control drug, are distinguishable in terms of initial dose and subsequent doses during the first weeks of the trial, a process will be applied to blind this information at the trial-team level.

Selected trial team members will be blinded to the treatment arm and dose of study drug of individual patients throughout the trial up to the database lock. All analyses and data review before database lock will be performed blindly, except for the study drug titration review, which will be performed by dedicated qualified persons.

The insulin titration review will be performed by examining the data related to fasting SMPG, hypoglycemia events, and study drug dose titration by dedicated, qualified persons.

The first statistical analysis plan (SAP) will be written before the first patient is randomized in the trial and will be finalized before database lock.

5.10 Study Drug Accountability and Adherence

Study drug accountability and adherence will be monitored at the time points specified in the SoE (Section 13.2).

Measures taken to ensure and document study drug accountability and adherence include the following:

- The treatment kit number should be properly recorded as required on the appropriate eCRF page, for accounting purposes.

- All treatment kits (whether empty or unused) are to be returned by the patient at each visit when treatment kit dispensing is planned.

- Patients will record their daily dose details in an eDiary (Section 13.3).

- The investigator (or their delegate) will track study drug accountability/adherence by comparing the treatment kit number captured in the electronic data collection (EDC) tool with the treatment/accountability log, eDiary information about daily doses, and the number of treatment kits provided versus the number of treatment kits returned (whether empty or unused).

- The monitor in charge of the trial will check the data entered on the study drug administration page in the eCRF and compare them with the study drug that has been returned and the patient's treatment log form.

5.11 Prior and Concomitant Therapy

A concomitant medication is any treatment received by the patient concomitantly to the study drug. Recording of prior and concomitant medications will be done at the time points specified in the SoE (Section 13.2).

Use of all concomitant medications will be recorded in the patient's eCRF. The minimum requirement is that the drug name and the dates of administration are be recorded; this includes all prescription drugs, herbal products, vitamins, minerals, and OTC medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Dose changes and any treatments in addition to the study drug should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the study drug, they may be given at the discretion of the investigator, with a stable dose (when possible). It is the responsibility of the investigator to ensure that details regarding the concomitant medication are recorded in full in the eCRF. The Gla-300 and IDeg-100 labels should be consulted for any additional information regarding concomitant medication administration.

The following medication(s) are not permitted during the screening and randomized, open-label treatment periods of the trial:

- Any type of glucose-lowering agents other than the study drug, protocol-allowed background noninsulin antidiabetic drug(s) (Section 5.2.1), and when applicable, rescue therapy (Section 5.2.2) are to be used. (Note: Short-term [≤10 days] use of short- or rapid-acting insulin therapy [eg, due to acute illness or surgery] is allowed.)
- Potential novel therapies like dual GIP and GLP-1 RA.
- Noninsulin antidiabetic drugs, which are not approved for combination with insulin according to local labeling/local treatment guidelines.
- Insulin pump therapy.
- Weight loss drugs (including OTC and herbal medications).
    - Patients who have initiated weight loss drugs (including OTC and herbal medications) within 3 months before the screening period should be excluded from the trial.
- Use of systemic glucocorticoids (excluding topical application or inhaled forms) for >14 consecutive days.
- Other medications are allowed as needed; however, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

6 Trial Assessments and Procedures

Before performing any procedures, all potential participants will sign an ICF (Section 9.3). They will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator will also sign the ICF.

The SoE is provided in Section 13.2.

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6.1 Efficacy Assessments

6.1.1 HbA1c Measurements

The primary efficacy endpoint and some secondary and exploratory endpoints will be assessed by HbA1c measurement. Blood samples will be collected to measure HbA1c at the different time points specified in the SoE (Section 13.2) at the central laboratory.

For the eligibility assessment, HbA1c levels will be measured during the screening period (Week –2, Visit 1). For the efficacy assessments of the trial, HbA1c levels will be measured at baseline/randomization, at the end of the titration period (Week 12; Visit 14), and at the end of the treatment period (Week 24, Visit 17; Section 13.2). If a patient needs to receive rescue antidiabetic therapy, the HbA1c assessment should be performed before they are introduced. In addition, in case of study drug treatment discontinuation, patients will be followed up per protocol. In case of trial discontinuation, HbA1c assessment will be performed at the time of withdrawal, if possible.

6.1.2 FPG Measurements

Blood samples will be collected to measure FPG levels at the time points specified in the SoE (Section 13.2) at the central laboratory. 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.

6.1.3 7-Point SMPG Profile

Patients will be supplied with a glucose meter and an eDiary during the screening period. Site staff will provide appropriate training to the patients on the proper use of the glucose meter and eDiary completion. The 7-point SMPG profile will be measured (and recorded in the patient's eDiary) at the following 7 points: preprandial and 2 hours after starting breakfast, lunch, and dinner, and at bedtime. The time points are specified in the SoE (Section 13.2).

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 (Section 13.2).

6.1.4 Fasting SMPG

Fasting SMPG values will be used to titrate and adjust study drug doses and monitor glycemic levels (Section 13.2). Patients 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; the results will be recorded in the eDiary.

During the trial period, additional glucose measurements can be done at the investigator's discretion.

6.1.5 SMPG During Symptomatic Hypoglycemia

Whenever patients experience hypoglycemia symptoms, they (or others, if applicable) should measure plasma glucose (using the glucose meter supplied during the screening period), if possible. Patients will be instructed to measure plasma glucose levels before carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected (Section 6.2.2), unless safety considerations necessitate immediate carbohydrate/glucose rescue before confirmation with the SMPG values.

Patients must contact the investigator as soon as possible after hypoglycemia events (especially, severe hypoglycemia events) for review and so that a decision can be made regarding any necessary actions. Patients should be instructed to again measure plasma glucose levels (using the glucose meter supplied during the screening period) once the event has resolved.

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6.2 Safety Assessments

6.2.1 Physical Examination

A physical examination will be performed, per standard of care to assess the health status of patients at the time points specified in the SoE (Section 13.2). Physical examination will include, at a minimum, assessment of the followings: general appearance, head, ears, eyes, nose, throat, neck, respiratory system, cardiovascular system, gastrointestinal system (including mouth), musculoskeletal system, central and peripheral nervous system, and skin.

6.2.2 Hypoglycemia Events

Hypoglycemia events will be assessed at the time points specified in the SoE (Section 13.2).

During the trial, patients 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 patient 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.

Hypoglycemia events will be evaluated based on the following categories of interest (Seaquist et al 2013; Agiostratidou et al 2017; American Diabetes Association [ADA] 2021):

- Overall hypoglycemia.
- Confirmed hypoglycemia (symptomatic, severe).
    - 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 patient such that the patient requires assistance from others.

*Note that "requires assistance" means that the person could not help themselves. Assisting a person out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

Clinical symptoms that are related to a hypoglycemia episode can include (but are not necessarily limited to) increased sweating, nervousness, asthenia, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, and coma (Agiostratidou et al 2017).

Any hypoglycemic event that leads to unconsciousness, coma, or seizure must be reported as an SAE. In addition, any hypoglycemic event, which at the investigator's discretion, qualifies as an SAE must also be reported as an SAE.

- 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).

- 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.

- 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.

- Nocturnal hypoglycemia: Any hypoglycemia of the above categories by:

    - Time of the day: Between 00:00 AM and 05:59 AM or 00:00 AM and 7:59 AM regardless of whether the patient was awake or work up because of the event.

    - Sleep status: Patient was asleep between bedtime and before getting up in the morning (ie, before the morning assessment of fasting prebreakfast SMPG and before any insulin injection). The patient wakes up because of the event.

    - Daytime hypoglycemia: Event that occurs between 06:00 and 23:59.

Hypoglycemia events will be classified and analyzed using the following variables:

- Percentage of patients with ≥1 episode(s) of confirmed hypoglycemia (cut-off value 70 mg/dL and 54 mg/dL) and event rate during the 24-week treatment period.

- Rate of hypoglycemia per patient-year computed as: 365.25/12 × (number of episodes of hypoglycemia)/(number of days exposed in time window).

- Percentage of patients and event rate of hypoglycemia by trial period (for ≤12 weeks, for >12 weeks to ≤24 weeks) to evaluate the potentially increased risk of hypoglycemia during the initial 12 weeks after initiating basal insulin treatment.

- The 24-hour (all time), daytime, and nocturnal (00:00 to 05:59, both inclusive) distribution of the occurrence of each episode of documented hypoglycemia by category, presented by 2-hour timeframe over 24 hours during the 24-week treatment period.

6.2.3 Local Tolerability at the Injection Site and Hypersensitivity Reactions

If the investigator or the patient recognizes any signs of local intolerability at the study drug injection site or hypersensitivity reactions, the event should be recorded in the AE page in the eCRF. If a patient reports severe injection site or hypersensitivity reaction between the site visits or during a phone call visit, the investigator or designee should ask them to come to the

site on the same or the next day, so that the event can be properly assessed, reported, and treated.

6.2.4 Vital Signs

Vital signs (including body weight, heart rate, SBP, and DBP) will be recorded at the time points specified in the SoE (Section 13.2). Height and body weight measurements at screening will be used to calculate BMI.

- Blood pressure (BP) will be assessed in a seated position using the same device (automated BP monitor or a manual sphygmomanometer) for each patient.
- Seated BP should be measured in both arms after at least a 5-minute rest, and then again after 1 minute in both arms while the patient is in a seated position. The arm with the highest SBP will be determined at this visit, and the BP should be measured using this arm throughout the trial. This highest value will be recorded in the eCRF.
- At subsequent visits, BP should be measured using the patients' designated arm, to be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).
- Heart rate (bpm) will be measured concurrently with the measurement of seated BP.

6.2.4.1 Body Weight

Body weight will be measured to assess the change from baseline to Week 24. While measuring their body weight, the patient should be wearing only undergarments or very light clothing and no shoes, and have an empty bladder.

The same weight scale should be used throughout the trial and calibrated on a regular basis as recommended by the manufacturer. Calibration should be documented in source documents by the site.

The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at "0" and the balance bar aligned. The patient should stand in the center

of the platform, as standing off-center may affect the measurement. The weights will be moved until the beam balances (the arrows are aligned). The weight should be read and recorded in the eCRF and source documents.

Self-reported weights are not acceptable; patients must not read the scales themselves.

6.2.5 Clinical Safety Laboratory Assessments

All clinical safety laboratory assessments (ie, hematology, clinical chemistry, urinalysis) will be performed by the central laboratory. The list of clinical safety laboratory tests to be performed is provided in Section 13.4. The timing and frequency of sample collection are provided in the SoE (Section 13.2).

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, notably, the disease progression of CKD) must be entered into the eCRF.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF.
- The laboratory reports must be filed with the source documents. Clinically significant, abnormal laboratory findings associated with the underlying disease or vital signs will not be considered clinically significant or be reported as AEs unless one of the following criteria is met:
    - Patient is symptomatic (and/or laboratory values are clinically significant per the investigator's discretion).
    - Patient requires corrective treatment or consultation.
    - Patient requires study drug treatment to be discontinued or modification of dosing.
    - Event fulfills a seriousness criterion.
    - Event meets the definition of an AESI (Section 6.2.6.2).

- 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.
    - If clinically significant values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 13.4, must be conducted in accordance with the laboratory manual and the SoE (Section 13.2).
- The recommended decision tree for the management of ALT increase is provided in Appendix 13.7.

6.2.6 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the trial, regardless of their relationship to the study drug or their clinical significance. The investigator remains responsible for following up on all AEs that are serious, considered related to the study drug or procedures, or caused the patient to discontinue the study drug treatment and/or the trial.

All AEs (serious or nonserious) will be recorded from the signing of the ICF until the safety follow-up visit, patient's permanent discontinuation from the trial, or loss to follow-up (Section 13.2).

The definitions of AEs and SAEs are provided in Section 13.5. The definition of an AESI is provided in Section 6.2.6.2.

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this be longer than 24 hours of awareness, as indicated in Section 6.2.6.5. The investigator will submit any updated SAE/AESI data to the sponsor or designee within 24 hours of receipt of the information.

After the AEs/SAEs (including AESIs) are initially reported, the investigator is required to proactively follow-up with each patient at subsequent visits/contacts. At the prespecified trial end date, all SAEs and AESIs will be followed up until resolution, stabilization, the event is

otherwise explained, or the patient is lost to follow-up (as defined in Section 4.4.2). Further information on follow-up procedures is provided in Section 13.5.3.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the trial. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and they consider the event to be reasonably related to the study drug or trial participation, the investigator must promptly notify the sponsor.

6.2.6.1 Suspected Unexpected Adverse Events

A suspected unexpected serious adverse reaction (SUSAR) is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information/labeling (eg, investigator's brochure [IB] for an unapproved study drug).

A "Dear Investigator" letter must be prepared for SUSARs according to local regulatory requirements and sponsor policy, and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the sponsor or designee will review and then file it along with the package insert and will notify the institutional review board (IRB)/independent ethics committee (IEC), if appropriate according to local requirements. It is the responsibility of the sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

6.2.6.2 Adverse Events of Special Interest

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 a trial by protocol amendment.

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

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

- Pregnancy will qualify as an SAE only if it fulfills one of the seriousness criteria (Section 13.5.2).
- If it is a pregnancy of a female patient, the study drug/NIMP should be discontinued.
- Follow-up of the pregnancy of a female patient or in a female partner of a male patient is mandatory until the outcome has been determined.

- Symptomatic overdose (serious or nonserious) with the study drug/NIMP.
  - An overdose (accidental or intentional) with the study drug/NIMP is an event suspected by the investigator or spontaneously reported by the patient and is defined as any dose administration that, in the investigator's opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin or is at least twice the intended dose within the intended therapeutic interval.
  - Asymptomatic overdose has to be reported as a standard overdose. The circumstances (ie, accidental or intentional) should be clearly specified verbatim on the form and symptoms, if any, must be entered on separate AE/SAE forms.
- Increase in ALT (>3 × ULN; see Section 13.7).

6.2.6.3 Pregnancy

A urine pregnancy test (only for WOCBP) will be performed at the time points specified in the SoE (Section 13.2).

To ensure patient safety, each pregnancy must be reported to sponsor or designee within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of mother and child, even if the patient was discontinued from the trial. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs. Spontaneous miscarriages must be reported as SAEs.

Any SAE occurring in association with a pregnancy that is brought to the investigator's attention after the patient has completed the trial and is considered by the investigator as possibly related to the study drug must be promptly reported to sponsor.

Any female patient who becomes pregnant while participating in the trial will be discontinued from study drug treatment.

6.2.6.4 Eliciting and Documenting AEs

Adverse events will be assessed from the time the patient signs the ICF until exit from the trial.

Serious AEs will be reported until 30 days after the last dose of study drug. Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the investigator considers them related to the study drug.

At every visit, patients will be asked a standard of nonleading questions to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to a patient's observations, AEs identified from any trial data (eg, laboratory values, physical examination findings) or identified from review of other documents (eg, the patient's eDiary) that are relevant to the patient's safety will be documented on the AE page in the eCRF.

6.2.6.5 Reporting AEs

All AEs reported or observed during the trial will be recorded on the AE page in the eCRF. Information to be collected includes dose, event term, time of onset, investigator-specified assessment of severity and relationship to the study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it changes during the trial, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 13.5.2) or an AESI (Section 6.2.6.2) must be reported to **PPD Pharmacovigilance** immediately (ie, within 24 hours) after the site personnel first learn about the event (Section 13.5.4).

6.2.6.6 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be rated as mild, moderate, or severe as described in Section 13.5.3.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of the onset and duration of each episode.

6.2.6.7 Assessment of Causality

The investigator's assessment of an AE's relationship to the study drug is part of the documentation process (Section 13.5.3), but is not a factor in determining what is or is not reported in the trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Related:	If the cause of the AE is related to the study drug/NIMP and cannot be reasonably explained by other factors, such as the patient's clinical state, concomitant therapy, and/or other interventions **OR** if the cause of the AE is unknown after a thorough review of the other factors.
Not Related:	When there is a clear alternative cause for the event other than the study drug/NIMP.

6.2.6.8 Follow-Up of Patients Reporting AEs

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable (Section 13.5.3).

6.2.7 Safety Monitoring Committee

An independent safety monitoring committee will not be formed for this trial. The medical monitor and sponsor will hold meetings at regular intervals to reviews all AEs.

6.2.8 Guidelines for Reporting Product Complaints

Recording of product complaints will be done at the time points specified in the SoE (Section 13.2).

Any defect in the study drug must be reported as soon as possible by the investigator to the monitoring team, which will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels, or documents [like pictures or photocopies]) related to product identification and to the potential deficiencies may need to be gathered. The investigator will assess whether the quality issue has to be reported together with an AE or SAE.

6.3 Sample Collections

Appropriately delegated site personnel will collect blood samples at the time points specified in the SoE (Section 13.2). These samples will be processed at the site and shipped the same day to the central laboratory, as specified in the laboratory manual. The central laboratory will analyze the blood samples for HbA1c and FPG measurements, clinical chemistry, and hematology. Results will be returned to the site within 48 to 72 hours.

6.4 Use of Biological Samples and Data For Future Research

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response, and toxicity and can help identify new drug targets or biomarkers that predict patient response to treatment. Therefore, data will be stored and used for future research when consented to by patients (Section 9.3) unless prohibited by local laws or IRBs (in such case, consent for future use of data will not be included in the local ICF).

For patients who consent to the storage and use of their data, data may be used after the trial ends for future research related to the study drug, the mechanism of action, the disease, or its associated conditions.

In the event future research is conducted for other purposes, trial patients will be informed of those purposes and will be given the means to object to those research projects.

Data will be used in compliance with the information provided to patients in the ICF Part 2 (future research).

All trial patient data will be coded such that no patient's directed identifiers will be linked to them. Coded data may be transferred to a sponsor site (or a subcontractor site) that may be located outside of the country where the trial is conducted. The sponsor adopts safeguards for protecting patient confidentiality and personal data (Section 10.2).

Trial patients' coded data will be stored for future research for up to 25 years after the end of the trial. If the data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a trial patient who has requested the destruction of their samples).

Patients' coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

7 Trial-Specific Committees

7.1 Steering Committee

The steering committee will be composed of key opinion leaders with clinical and methodological expertise in diabetes, renal disease, and the conduct of clinical trials. This committee, led by a chairman, will have the following roles and responsibilities:

- Providing input into the development of the protocol and in some cases, of any subsequent amendments.
- Assisting in decisions for protocol amendments (or making recommendations).
- Assisting with the overall supervision of the trial, including (but not limited to) the following tasks:
    - Participating in virtual investigators' meeting.
    - Assessing global trial progress in conjunction with the sponsor team.
    - Analyzing and interpreting study data.
    - Assisting with resolution of site issues that arise over the course of the trial (as necessary) to assure quality trial conduct.
    - Supporting/endorsing sponsor responses to regulatory authority inquiries (as necessary).
    - Validating the main features of the SAP.
    - Communicating with the investigator sites, including (but not limited to) major trial milestones or decisions.
    - Providing other input, such as editorials in newsletters to be sent to site investigators (if needed).

- Supporting trial publications with the following tasks:
    - Defining the overall publication plan, including the primary publications reporting new scientific findings/data from the trial.
    - Reviewing and approving (or abstain from) all other proposed publications and draft manuscripts regarding subsequent publications, including local publications.

8 Statistical Considerations

The statistical considerations summarized in this section outline the plan for data analysis in this trial. Details of the analyses to be conducted will be specified in an SAP, which will be finalized and approved before database lock. Changes from the analyses planned in this protocol will be documented in the SAP.

8.1 Estimands and Intercurrent Events

8.1.1 Intercurrent Events

The relevant intercurrent event (ICE) types in this trial are presented in Table 8-1.

Table 8-1 Intercurrent Events

Label	Intercurrent Event Types
ICE1 (Discontinuation due to any reasons)	Discontinuation of study drug treatment due to any reasons
ICE2 (Rescue therapy)	Use of rescue therapies

Abbreviation: ICE, intercurrent event.

8.1.2 Estimands

Attributes for the primary and supplementary estimands with the strategies used for handling ICEs are presented in Table 8-2.

Table 8-2 Primary and Supplementary Estimands

	Estimand 1a (Primary)
Estimand Description	Difference in the mean change from baseline to Week 24 in HbA1c level (Gla-300 vs IDeg-100) in insulin-naïve patients 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 reasons and use of rescue therapies
Target Population	Insulin-naïve patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable) as defined by the inclusion/exclusion criteria (Section 4)
Treatment Conditions	Once daily, SC self-injection of Gla-300 versus IDeg-100 with the planned dose modifications outlined in Section 5.5.1 • Gla-300: Insulin glargine 300 U/mL • IDeg-100: Insulin degludec 100 U/mL
Endpoint	Change in HbA1c level from baseline to Week 24
Population Level Summary	Difference in the mean change in HbA1c level from baseline to Week 24 between Gla-300 and IDeg-100

	Estimand 1a (Primary)
ICEs and Strategies	**Treatment policy strategy** for handling the ICEs in Table 8-1
Rationale	Using the treatment policy strategy for handling ICEs is considered appropriate for showing superiority (ICH E9 R1), which allows switching the objective of a trial from non-inferiority to superiority (CPMP guideline)
	Estimand 1b (Supplementary)
Estimand Description	Difference in the mean change from baseline to Week 24 in HbA1c level (Gla-300 vs IDeg-100) in insulin-naïve patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable), assuming no discontinuation of study drug treatment due to any reasons and use of rescue therapies
Target Population	Insulin-naïve patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable) as defined by the inclusion/exclusion criteria (Section 4)
Treatment Conditions	Once daily, SC self-injection of Gla-300 versus IDeg-100 with the planned dose modifications outlined in Section 5.5.1 • Gla-300 arm: Insulin glargine 300 U/mL • IDeg-100 arm: Insulin degludec 100 U/mL
Endpoint	Change in HbA1c level from baseline to Week 24
Population Level Summary	Difference in the mean change in HbA1c level from baseline to Week 24 between Gla-300 and IDeg-100
ICEs and Strategies	**Hypothetical strategy** for handling the ICEs in Table 8-1
Rationale	Using the hypothetical strategy for handling ICEs is considered conservative and relevant for demonstrating non-inferiority. This supplementary estimand will only be estimated for supporting the non-inferiority analysis

Abbreviations: CPMP, committee for proprietary medicinal products; Gla-300, insulin glargine 300 U/mL; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; ICE, intercurrent event; ICH, International Council for Harmonisation; IDeg-100, insulin degludec 100 U/mL; OAD, oral antidiabetic drug; SC, subcutaneous; T2DM, type 2 diabetes mellitus.

8.2 Statistical Hypothesis

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

8.3 Sample Size Determination

This trial is designed with a primary objective of demonstrating that Gla-300 is non-inferior to IDeg-100 regarding change from baseline to Week 24 in HbA1c level, with a non-inferiority margin of 0.3%, a 2.5% alpha risk (1-sided), and 90% power, assuming an SD of 1.1 and 10% dropouts. 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 (EMA 2018).

A sample size of 566 randomized patients (283 per treatment arm with a 1:1 allocation ratio) is expected to ensure that the upper bound of the 2-sided 95% CI for the difference in the mean change from baseline to Week 24 in HbA1c level between Gla-300 and IDeg-100 would not exceed the non-inferiority margin of 0.3% with approximately 90% power. This calculation assumes a common SD of 1.1% with a 1-sided test at the 2.5% significance level and that the true difference in the mean change between Gla-300 and IDeg-100 is 0. Assuming a 10% dropout rate, a total of 630 patients 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 the nQuery Software Version 7.0.

8.4 Analysis Sets

The following analysis sets will be used in the statistical analyses:

- Safety set: The safety set will consist of all patients 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.

- Intention-to-treat (ITT) set: The ITT set will consist of all patients who sign the ICF and are randomized into the trial. All analyses using the ITT set will group patients according to their randomized treatment.

- Per protocol set (PPS): The PPS will consist of all randomized patients who complete the trial without major protocol deviations.

The ITT set will be used for the primary efficacy analyses, the PPS will be used for a supportive analysis for non-inferiority, and the safety analyses will be based on the safety set. Patients' disposition will be presented for the ITT set.

8.5 Description of Subgroups to be Analyzed

Subgroup analyses will be performed by:

- 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/1.73m^2; ≥45 mL/min/1.73m^2)

Details of these and other possible subgroup analyses will be specified in the SAP.

8.6 Disposition, Demographics, and Baseline Characteristics

Summary statistical analyses will be provided for demographics, baseline disease characteristics, medical history, and other characteristics.

Patient disposition will be summarized by study drug treatment and include the number of patients in the safety set who completed or withdrew from the study drug treatment, as well as the number of patients in each analysis set.

The number of patients who withdrew from study drug treatment and withdrew from the trial will be summarized by study drug treatment and the reason for withdrawal.

8.7 Statistical Analysis Methodology

8.7.1 General Considerations

Statistical analyses will be performed using SAS software Version 9.4 or higher. Continuous variables will be summarized using the mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

All CIs presented will be 2-sided 95% CIs, unless otherwise specified. For the primary efficacy endpoint, non-inferiority will be established 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). If non-inferiority is demonstrated, superiority of Gla-300 to IDeg-100 will also be considered and established if the 95% CI 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 8.1.2. There is no multiplicity argument that affects switching between non-inferiority and superiority, since it corresponds to a simple closed testing procedure.

No multiplicity adjustment will be made on the secondary and exploratory endpoints. When presented, 95% CIs and nominal *P* values, will be provided for descriptive purpose only.

Details of the statistical analyses, methods, and data conventions will be described in the SAP.

8.7.2 Overview of Statistical Methods: Estimation of Primary Estimands and Sensitivity Analyses

Table 8-3 presents a summary of the statistical methods, including the sensitivity/supportive analyses.

Table 8-3 Summary of Statistical Methods for Primary Estimands

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data Censoring Rules**	**Analysis Model/Method**	**Sensitivity/Supportive Analysis**
Estimand 1a (Primary)	Difference in the mean change from baseline to Week 24 in HbA1c level (Gla-300 vs IDeg-100) in insulin-naïve patients 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 and use of rescue therapies	ITT	Data collected after ICEs will be included.	An MI strategy and an ANCOVA model including baseline HbA1c value as a covariate, and study drug treatment and stratification factors at randomization (other than categorized HbA1c) as fixed factors. Details are provided in Section 8.7.3.1.	An MMRM will be used as a sensitivity analysis including study drug treatment, visit, and stratification factors at randomization as fixed factors, baseline HbA1c value as a covariate, and treatment-by-visit and baseline HbA1c value-by-visit interactions. Least-squares means and differences with 95% CIs and *P* values at each time point will be presented. Reference-based MI (sensitivity analysis for superiority only): MI will be performed assuming that the trajectory of withdrawals from the Gla-300 arm is the same

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data Censoring Rules**	**Analysis Model/Method**	**Sensitivity/Supportive Analysis**
					as that in the IDeg-100 arm. Penalized MI (sensitivity analysis for non-inferiority only): Imputed missing data at Week 24 in the primary analysis will be penalized by adding 0.3% in the Gla-300 arm, and imputed values in the IDeg-100 arm will not be penalized.
Estimand 1b (Supplementary)	Difference in the mean change from baseline to Week 24 in HbA1c level (Gla-300 vs IDeg-100) in insulin-naïve patients with T2DM and renal impairment who have glycemic levels above target with OADs with or without GLP-1 RA (oral or injectable), assuming no discontinuation of study drug treatment due to any reasons and use of rescue therapies	ITT	Data collected after the ICEs will be excluded from the analysis.	An MMRM will be performed including study drug treatment, visit, and stratification factors at randomization as fixed factors, baseline HbA1c value as a covariate, and treatment-by-visit and baseline HbA1c value-by-visit interactions. Least-squares means and differences with 95% CIs and *P* values at each time point will be presented; this estimand will only be estimated to support non-inferiority.	Per-protocol analysis based on the PPS will be performed as a supportive analysis for non-inferiority.

Abbreviations: ANCOVA, analysis of covariance; Gla-300; insulin glargine 300 U/mL; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; ICE, intercurrent event; IDeg-100, insulin degludec 100 U/mL; ITT, intention-to-treat; MI, multiple imputation; MMRM, mixed-effect model with repeated measurements; MAR, missing at random; OAD, oral antidiabetic drug; PPS, per protocol set; T2DM, type 2 diabetes mellitus.

8.7.3 Analysis of Primary Endpoints

8.7.3.1 Main Estimation of Primary Estimand

For the primary efficacy endpoint (ie, change from baseline to Week 24 in HbA1c level), data collected after the ICEs will be included in the analysis based on the ITT set. Missing data will be handled using a multiple imputation (MI) strategy depending on treatment-completion status:

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

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

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 imputed datasets with monotone missing data pattern obtained from Step 1, missing data will then be imputed using the sequential regression method.

The imputation model for Step 1 will include the treatment arm, baseline HbA1c value, and HbA1c values at Week 12 and Week 24. The imputation model for Step 2 will include the same variables as in Step 1 with the randomization strata (other than the categorized HbA1c).

For each multiply imputed dataset, an analysis of covariance (ANCOVA) model will be performed; this analysis will include baseline HbA1c value as a covariate, and study drug treatment and stratification factors at randomization (other than the categorized HbA1c) as fixed factors. 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. The estimated differences and their SDs obtained across the imputed datasets will be combined to produce a single point estimate and CI using Rubin's rule and presented with a 2-sided 95% CI and a *P* value.

The tests 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 difference 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%.

8.7.3.2 Sensitivity Analysis of Primary Estimand

Sensitivity analyses will be conducted for the ITT to assess the robustness of the results obtained from the primary analysis.

Mixed-Effect Model with Repeated Measurements Analysis

A mixed-effect model with repeated measurements (MMRM) analysis will be used as a sensitivity analysis; this analysis will include study drug treatment, visit, and stratification factors at randomization (other than the categorized HbA1c) as fixed factors, 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-patient errors. 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 mean difference between treatment arms (Gla-300 vs IDeg-100) will be estimated based on the LS means for the treatment-by-visit interaction in the MMRM model. The estimates will be presented together with *P* values and 95% CIs at Week 24.

Penalized Multiple Imputation (For Non-Inferiority Only)

The 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. The treatment differences and their SDs estimated from each imputed dataset will be combined using Rubin's rule for a single estimate and its associated 95% CI.

Reference-Based Multiple Imputation (For Superiority Only)

The reference-based MI assumes that the trajectory of withdrawals from the Gla-300 arm due to any reason is the same as that in the IDeg-100 arm, and imputes the missing HbA1c values in the Gla-300 arm using the imputation model established based on the data in the IDeg-100 arm.

The details of the imputation procedures will be specified in the SAP.

8.7.3.3 Main Estimation of Supplementary Estimand

The supplementary estimand will be estimated to support non-inferiority only. For this estimand, data collected after the ICEs will be excluded from the analysis based on the ITT set. An MMRM will be performed for the Hb1Ac values at Week 12 and Week 24; this will include study drug treatment, visit, and stratification factors at randomization (other than the categorized Hb1Ac) as fixed factors, 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-patient 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 and differences with 95% CIs and *P* values at each time point will be presented.

8.7.3.4 Supportive Analysis of Supplementary Estimand

A per-protocol analysis based on the PPS will be performed as a supportive analysis for non-inferiority. An ANCOVA will be performed as described for the primary analysis. No imputation of missing data will be needed, as patients with missing Week 24 measurements will be excluded from the PPS.

8.7.4 Analysis of Secondary Endpoints

All secondary endpoints will be analyzed for the ITT set, in a similar manner as for the primary estimand. The continuous secondary endpoints will be analyzed using the same approach as described for the primary endpoint above, including the baseline values for the corresponding endpoint as covariates. All stratification factors at randomization will be included as fixed factors.

For the categorical secondary efficacy endpoint (patients reaching HbA1c target of <7.0% at Week 24), if a patient has a missing HbA1c value at Week 24, it will be assumed that they did not reach an HbA1c target of <7.0%. A logistic regression model adjusting for treatment arm and stratification at randomization (other than the categorized HbA1c) and HbA1c at baseline will be performed. The odds ratio (OR) estimated from the model will be presented together with its 95% CI.

8.7.5 Analyses of Exploratory Endpoints

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Analysis of the CGM Substudy Exploratory Endpoints

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8.7.6 Analysis of Safety Evaluation

All safety analyses will be performed on the safety set. The summary of safety results will be presented by treatment arms.

8.7.6.1 Analysis of AEs

The observation period of safety data will be divided as follows:

- The pre-treatment period 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-week on-treatment period) is defined as 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).
- The post-treatment period is defined as the time starting 8 days after the last injection of the open-label study drug (after on-treatment period).

The AE observations will be classified per the observation periods of safety data (as defined above) into:

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

All AEs will be coded to a “preferred term” (PT) and “high-level group term” (HLGT), “high-level term” (HLT) and primary “system organ class” (SOC) using the version of MedDRA currently in use by the sponsor at the time of database lock.

Adverse event incidence tables will present data by SOC (sorted by internationally agreed order), HLGT, HLT, and PT sorted in alphabetical order for each treatment arm, as well as the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment

phase. The denominator for computation of percentages is the safety set within each treatment arm.

The AE incidence tables will be provided by treatment arm for all types of TEAEs: All TEAEs, all treatment-emergent SAEs, all TEAEs leading to permanent treatment discontinuation, and all TEAEs related to local tolerability at injection site, and hypersensitivity.

The following death summaries will be generated for the safety set:

- Number (%) of patients who died by trial period (TEAE periods, on-trial, post-trial) and reasons for death, summarized by treatment received.
- Death in nonrandomized patients or randomized patients who were not treated.

Treatment-emergent AEs leading to death (as an outcome on the AE eCRF page as reported by the investigator) will be summarized by primary SOC, HLGT, HLT, and PT showing the number (%) of patients. The summary table will be sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

8.7.6.2 Hypoglycemia

The number and incidence of patients experiencing at least 1 hypoglycemic event will be presented by treatment arm and type of hypoglycemic event (ADA category) according to the diurnal distribution.

The ORs and corresponding 95% CIs of the Gla-300 arm compared with the IDeg-100 arm will be estimated for each hypoglycemic event using a logistic regression model that includes treatment arm and stratification factors at randomization as fixed factors based on observed cases.

The number and rate of hypoglycemic events (in patient-month of exposure) will be determined by treatment arm and type of hypoglycemic event (ADA category), according to the diurnal distribution. For each hypoglycemic event, the rate ratios and corresponding 95% CIs of the Gla-300 arm over the IDeg-100 arm will be estimated using a negative-binomial regression adjusted for stratification factors at randomization with time on treatment as an offset.

The number and incidence of patients experiencing at least 1 nocturnal hypoglycemic event defined by sleep status and the number and rate of these nocturnal events (in patient-month of exposure) will also be presented by treatment arm.

The aforementioned hypoglycemia analyses will be performed and presented separately for the overall 24-week study treatment period, the titration period (ie, Week 1 through Week 12), and the maintenance period (ie, Week 13 through Week 24).

8.7.6.3 Other Safety Analyses

The clinical safety laboratory test values, vital signs, and physical examination findings will be summarized by treatment arm. Potential clinically significant values will be flagged and summarized.

8.7.7 Other Analyses

Descriptive summary analyses will be provided for medical history and risk factor variables at baseline.

The extent of study drug treatment exposure and compliance will be descriptively summarized by treatment for the safety set.

8.8 Handling of Missing Data

Details on how missing dates for AEs or concomitant medications will be handled will be specified in the SAP.

For the primary analysis, an MI strategy (as specified in Section 8.7.3.1) will be used for handling missing data. An MMRM assuming missing at random (MAR) will be used as a sensitivity analyses. A reference-based MI strategy assuming missing not at random (MNAR) will be performed as a sensitivity analysis for superiority. The details of missing data handling will be specified in the SAP.

8.9 Interim Analyses

No interim analyses are planned for this trial.

8.10 Data Quality Assurance

- All patient data relating to the trial will be recorded on printed case report forms (CRFs) or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- Guidance on completion of CRFs will be provided in a set of CRF Completion Guidelines.

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate trial documents.

- The sponsor or designee is responsible for the data management of this trial, including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after the signature of the final trial report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

8.10.1 Data Management

As part of the responsibilities assumed by participating in the trial, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as

part of the case histories. These source documents may include medical charts, the patient's eDiary, and laboratory reports (Section 13.8).

PPD will supply the eCRF, whose access will be limited to personnel directly participating in the trial, and all eCRFs should be completed in English.

All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated per the guidelines for completion. Blank spaces should not be present unless otherwise directed.

Clinical data management will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events and concomitant medication terms will be coded using MedDRA and WHODrug, respectively. After database lock, each site will receive their site-specific eCRF data as entered into Medidata Rave for the trial, including full discrepancy and audit history. Additionally, a copy of all data from the trial will be created and sent to the sponsor for storage. In all cases, patient initials and their date of birth will not be collected.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before trial onset, any information related to this trial or provided to the patient (eg, the protocol, informed consent, advertisements for recruitment of trial participants, any other written information) must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the trial at intervals not exceeding 1 year or otherwise specified by the IRB/IEC.
The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the trial or increasing the risk to patients.

9.2 Ethical Conduct of the Trial

The trial will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

9.3 Patient Information and Consent

A written informed consent in compliance with regulatory authority regulations and/or US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the trial or performing any unusual or nonroutine procedure. An informed consent template will be provided by the sponsor to investigative sites. If any institution-specific modifications to trial-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before submitting the

revised ICF to the IRB/IEC. If the ICF is revised during the course of the trial, all active patients must sign the revised form.

Before recruitment and enrollment, each potential patient will be given a full explanation of the trial and be allowed to read the approved ICF. Once the investigator is assured that the patient understands the implications of participating in the trial, the patient will be asked to give consent to participate in the trial by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the trial but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the sponsor, its designee, regulatory authorities (eg, the US FDA), or the IRB/IEC.

The investigator and all employees and coworkers involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Written agreement from the sponsor or its designee must be obtained before the disclosure of any said confidential information to other parties.

10.2 Data Protection

All personal data collected and/or processed in relation to this trial will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the General Data Protection Regulation (GDPR). The trial sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the investigator and/or to the patients, the sponsor will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of Patient Data

The data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the trial objective.

This trial will attempt to represent a diverse set of patients with T2DM and renal impairment, as they represent a growing proportion of the patient population, are historically under-represented in clinical trials, and are disproportionately affected by T2DM and renal impairment. For example, ethnic minority groups are known to have a higher prevalence of T2DM and end-stage renal failure compared with the white majority population (Mathur et al 2018).

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Protection of Data Related to Professionals Involved in the Trial

- Personal data (eg, contact details, affiliation details, job title and related professional information, role in the trial, professional resume, training records) are necessary to allow Sanofi to manage involvement in the trial and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.

- Personal data can be processed for other trials and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).

- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi trial. In case the professionals have already been involved in a Sanofi trial, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies' disqualification list.

- Personal data can be communicated to the following recipients:

    - Personnel within Sanofi or partners or service providers involved in the trial.

    - Judicial, administrative, and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law, including the following:
    - The standard contractual clauses of the European Commission for transfers towards our partners and service providers.
    - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals are able to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to 30 years unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of investigators' personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows investigators to keep their data up-to-date once, for access by all pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request access to and rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.3 Financial Disclosure and Obligations

Investigators and sub-investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements per requirements of local or national regulatory authorities and/or under 21 CFR 54.

In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the trial.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the patient's disease.

10.4 Investigator Documentation

Before beginning the trial, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and Title 21 of the CFR and/or with local or national regulatory requirements by providing all essential documents, including but not limited to the following:

- IRB/IEC approval.
- Original investigator-signed agreement page of the protocol.
- Curriculum vitae for the investigator and each sub-investigator.
- Financial disclosure information to allow the sponsor or designee to submit complete and accurate certification. In addition, investigators must provide to the sponsor or designee a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the trial.
- IRB-/IEC-approved informed consent, samples of site advertisements for recruitment for this trial, and any other written information regarding this trial that is to be provided to the patient.
- Signed Clinical Trial Agreement.

10.5 Trial Conduct

The investigator agrees that the trial will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this trial in accordance with all national, state, and local laws or regulations. Trial information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

10.6 Adverse Events and Trial Report Requirements

The investigator agrees to submit reports of SAEs to the sponsor or designee and/or IRB/IEC according to the timeline and method outlined in the protocol (Section 13.5.4). In addition, the investigator agrees to submit annual reports to the site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and the sponsor and regulatory authority(ies) with any reports required.

11 Trial Management

11.1 Monitoring

11.1.1 External Data Monitoring Committee

No data monitoring committee is planned for this trial.

11.1.2 Monitoring of the Trial

The clinical monitor, as a representative of the sponsor, has the obligation to follow the trial closely. In doing so, the monitor will visit the investigator and site at periodic intervals, in addition to maintaining necessary phone and letter contact. The monitor will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the investigator and personnel.

In the event a clinical monitor cannot visit the site in a timely manner due to the coronavirus disease 2019 (COVID-19) pandemic, alternative monitoring approaches, such as remote source data verification may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local health authority, privacy laws, and permitted by the IRB/IEC.

The medical monitor and sponsor will hold meetings at regular intervals to review AEs, unless an SAE is noted and reported as described in Section 6.2.6.5.

All aspects of the trial will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the trial will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all trial records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, US FDA) access to all trial records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patients, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to local regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the trial (Section 4.4).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of protocol deviations as applicable.

11.3 Trial Termination

Although sponsor has every intention of completing the trial, they reserve the right to discontinue the trial at any time for clinical or administrative reasons.

The end of the trial is defined as the date of the last visit of the last patient in the trial globally.

11.4 Final Report

Whether the trial is completed or prematurely terminated, the sponsor will ensure that the clinical study report (CSR) is prepared and provided to the regulatory agencies as required by the applicable regulatory requirements. The sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where applicable by regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete trial results.

Upon completion of the CSR, the sponsor will provide the investigators with the full summary of the trial results. The investigators are encouraged to share the summary results with the trial patients, as appropriate. The trial results will be posted on publicly available clinical trial registers.

11.5 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

11.6 Publication Policy, Disclosure, and Clinical Trial Registration

11.6.1 Publication Policy and Disclosure

- The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement between the sponsor and the investigator and in line with International Committee of Medical Journal Editors authorship requirements.

11.6.2 Clinical Trial Registration

In order to ensure that information regarding clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, sponsor (or its designee) will register interventional clinical trials it sponsors globally on ClinicalTrials.gov or other publicly accessible registers (eg, EudraCT) before the start of the trial.

11.6.3 Clinical Trial Results Disclosure

Trial Patients

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu/), and sanofi.com, as well as national registries, as applicable.

In addition, results from clinical trials in patients are required to be submitted to peer reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual patient data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of patients in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals Involved in the Trial or in the Drug Development Program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation, or by a code of conduct, such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations."

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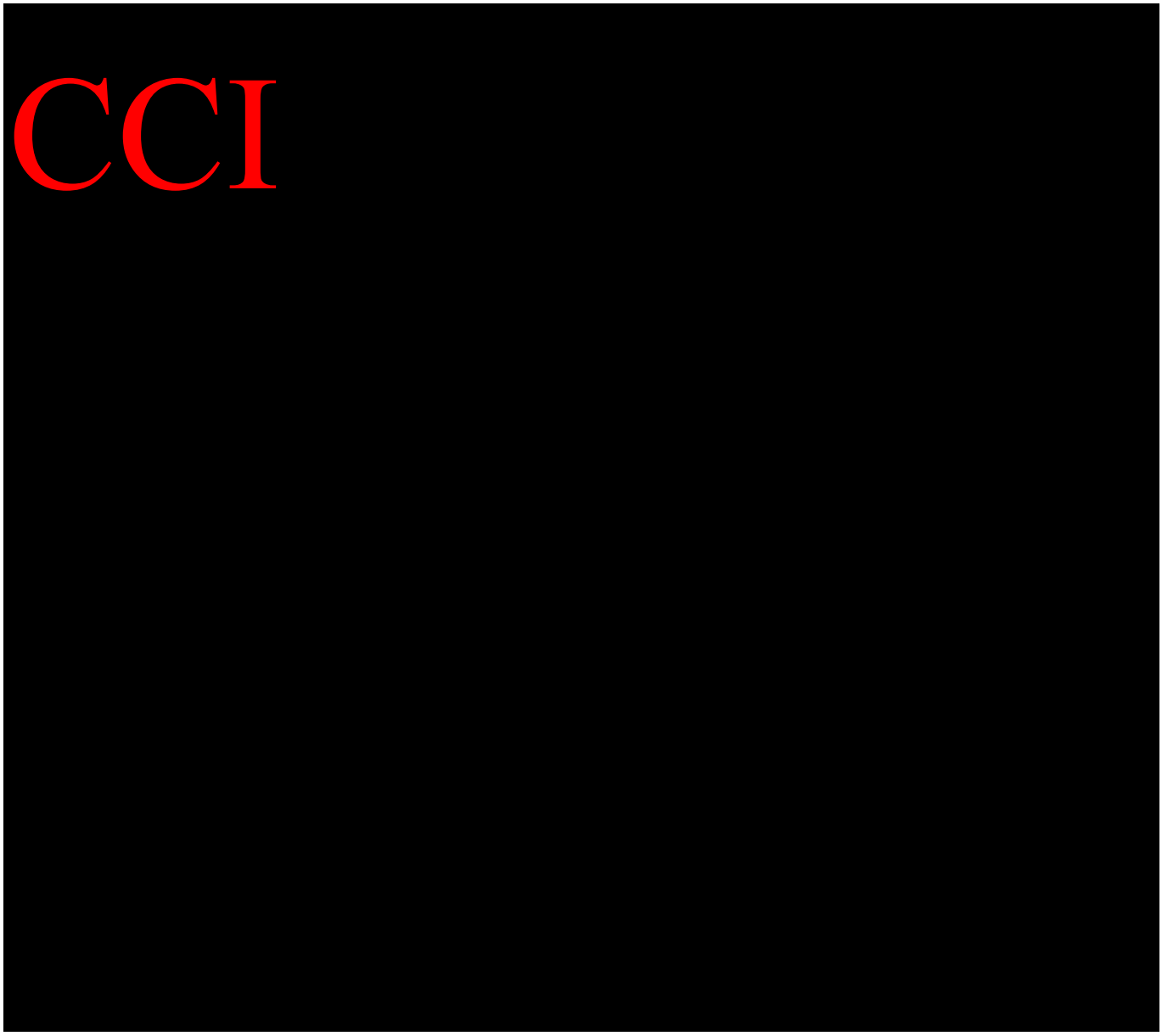
13 Appendices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13.2 Appendix: Schedule of Events for the Main Trial

Table 13-3 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]		

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**
Pregnancy test[q]	X			X				X			X		

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; CGM, continuous glucose monitoring; 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 (Table 5-2). 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.

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[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.

[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: preprandial 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 6.2.2.

[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 13.4). 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] (National Kidney Foundation 2022).

[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.

13.3 Appendix: Patient eDiary Information

Patients will be provided with an eDiary to use during the trial, and site staff will instruct them on how to complete the eDiary. Training on eDiary use will be documented in the patient's source documents.

Patients are required to make eDiary entries at least once daily from the screening period (Visit 1) through the end of the treatment period (Visit 17) and bring completed eDiaries at each site visit. Site staff will verify the eDiary (at the time points specified in the SoE [Section 13.2]) by viewing the data transmitted from the eDiaries into the database.

The information to be recorded in the eDiary may include, but not be limited to, the following:

- Each dose of study drug taken (date/time and actual dose) and type and dose of daily background noninsulin antidiabetic drug(s). The patient will document any temporary treatment discontinuations.
- 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.
- 7-point SMPG profile: 7-point SMPG profiles measured at the following 7 points: preprandial and 2 hours after starting breakfast, lunch, and dinner, and at bedtime. The time points are specified in the SoE (Section 13.2).
- Symptoms of hypoglycemia: Patients will be trained on the hypoglycemia eDiary completion requirements and the need to contact the investigator as soon as possible in case of a significant hypoglycemia occurrence, so that appropriate actions can be taken (eg, intolerance to the study drug injection).
- If assistance to resolve the hypoglycemia event was required out of necessity or convenience.

13.4 Appendix: Clinical Safety Laboratory Tests

- The tests detailed in Table 13-4 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.

- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 4 of the protocol.

- 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 notably, the disease progression of CKD) must be entered into the eCRF.

Table 13-4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments[a]	Parameter
Hematology	Erythrocytes
	Platelet count
	Leukocytes
	Hb
	Hematocrit
Clinical chemistry	AST
	ALT
	Alkaline phosphatase
	Total bilirubin (if >ULN, then the direct and indirect subfractions must be measured)
	Albumin (serum)
	Creatinine (serum)[b]
	Spot urine albumin: creatinine ratio[b]
	eGFR[b,c]
	Sodium
	Potassium
Urinalysis	pH
	Glucose
	Ketones
	Leukocytes
	Blood/Hb
	Protein

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cr, creatinine; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; MDRD, Modification of Diet in Renal Disease; Scr, serum creatinine; ULN, upper limit of normal.

[a] All protocol-required safety laboratory assessments will be performed at the central laboratory, except urine pregnancy tests, which will be performed locally; the results of each test must be entered into the eCRF.

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

[c] 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] (National Kidney Foundation 2022).

13.5 Appendix: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

13.5.1 Definition of AEs

- An AE is any untoward medical occurrence in a patient or clinical trial patient, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated).

Events <u>Meeting</u> the AE Definition

- Any abnormal laboratory test results (eg, hematology, clinical chemistry, urinalysis) or other safety assessments (eg, vital sign measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease), eg, that meet the following criteria:
    - Are symptomatic.
    - Require corrective treatment or consultation.
    - Lead to study drug discontinuation.
    - Fulfill a seriousness criterion.
    - Meet the definition of an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition, including an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the trial.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of study drug or a concomitant medication.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

13.5.2 Definition of SAEs

An SAE is defined as any AE that, at any dose, meets one of the following criteria:

- **Results in death.**

- **Is life-threatening.**

    - The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization.**
    - In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity.**
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect.**
- **Other situations.**
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Chronic neurodegenerative diseases diagnosed during the trial.
- Cancers diagnosed during the trial.
- Bullous cutaneous eruptions.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Suicide attempt or any event suggestive of suicidality.
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN.
- Allergic bronchospasm, convulsions. (seizures, epilepsy, epileptic fit, absence, etc.).
- Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.).

13.5.3 Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the patient's medical records to the sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor's representative. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the sponsor's representative.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between the study drug/NIMP and each occurrence of an AE/SAE (including AESI).
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE/SAE (including AESI), the investigator must document in the medical notes that they have reviewed the AEs/SAEs (including AESIs) and have provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE/AESI data to the sponsor or designee.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor's representative to elucidate the nature and/or causality of the AEs or SAEs (including AESIs) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a patient dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor's representative with a copy of any post-mortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.

- The investigator will submit any updated SAE/AESI data to the sponsor or designee within 24 hours of receipt of the information.

13.5.4 Reporting of SAEs, Including AESIs

SAE/AESI Reporting to the Sponsor via an EDC Tool

- The primary mechanism for reporting an SAE/AESI to the sponsor's representative (ie, PPD Pharmacovigilance) will be the EDC tool.
- If the electronic system is unavailable, then the site will use the backup paper SAE/AESI data collection tool (see the following section) to report the event within 24 hours.
- The site will enter the SAE/AESI data into the electronic system as soon as it becomes available.
- After the trial is completed at a given site, access to the EDC tool will be reduced to read-only or revoked to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE/AESI from a trial patient or receives updated data on a previously reported SAE/AESI after access to the EDC tool has been reduced (read-only or revoked), then the site can report this information on a paper SAE/AESI form (see the following section) or to the sponsor's representative by fax.
- Contacts for SAE reporting can be found in the Investigator's Trial File.

SAE/AESI Reporting to the Sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE/AESI paper data collection tool is the preferred method to transmit this information to the sponsor's representative.
- In the unlikely event of EDC downtime, the paper forms must be used for reporting of events that require expedited reporting (SAEs/AESIs). Paper forms should be faxed to PPD Pharmacovigilance at CCI [redacted]
- Initial notification via fax does not replace the need for the investigator to complete and sign the SAE/AESI data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator's Trial File.

13.6 Appendix: Contraceptive and Barrier Guidance

Definitions:

Woman of Childbearing Potential

- A woman is considered a WOCBP (fertile) from the time of menarche until becoming postmenopausal (as follows) unless permanently sterile (as follows).
- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen-hormonal, highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

Permanent sterilization methods include:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.
- For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determine trial eligibility.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study drug, additional evaluation should be considered.

Woman of Nonchildbearing Potential

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one of the following:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.
    - For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining trial eligibility.
2. Postmenopausal female.

A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE THE FOLLOWING:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation.[c]
• Intrauterine device (IUD).
• Intrauterine hormone-releasing system (IUS).[c]
• Bilateral tubal occlusion.
• Azoospermic partner (vasectomized or due to a medical cause). *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: Documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.[c] • Oral • Intravaginal • Transdermal • Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation.[c] • Oral • Injectable

Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the patient.*
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. [b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. [c] Male condoms must be used in addition to hormonal contraception. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this trial. Male condom and female condom should not be used together (due to risk of failure from friction).

Collection of Pregnancy Information

Male Patients With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this trial. This applies only to male patients who receive the study drug.

- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

- The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this trial. The initial information will be recorded on the appropriate form and submitted to the sponsor or designee within 24 hours of learning of a patient's pregnancy.

- The patient will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

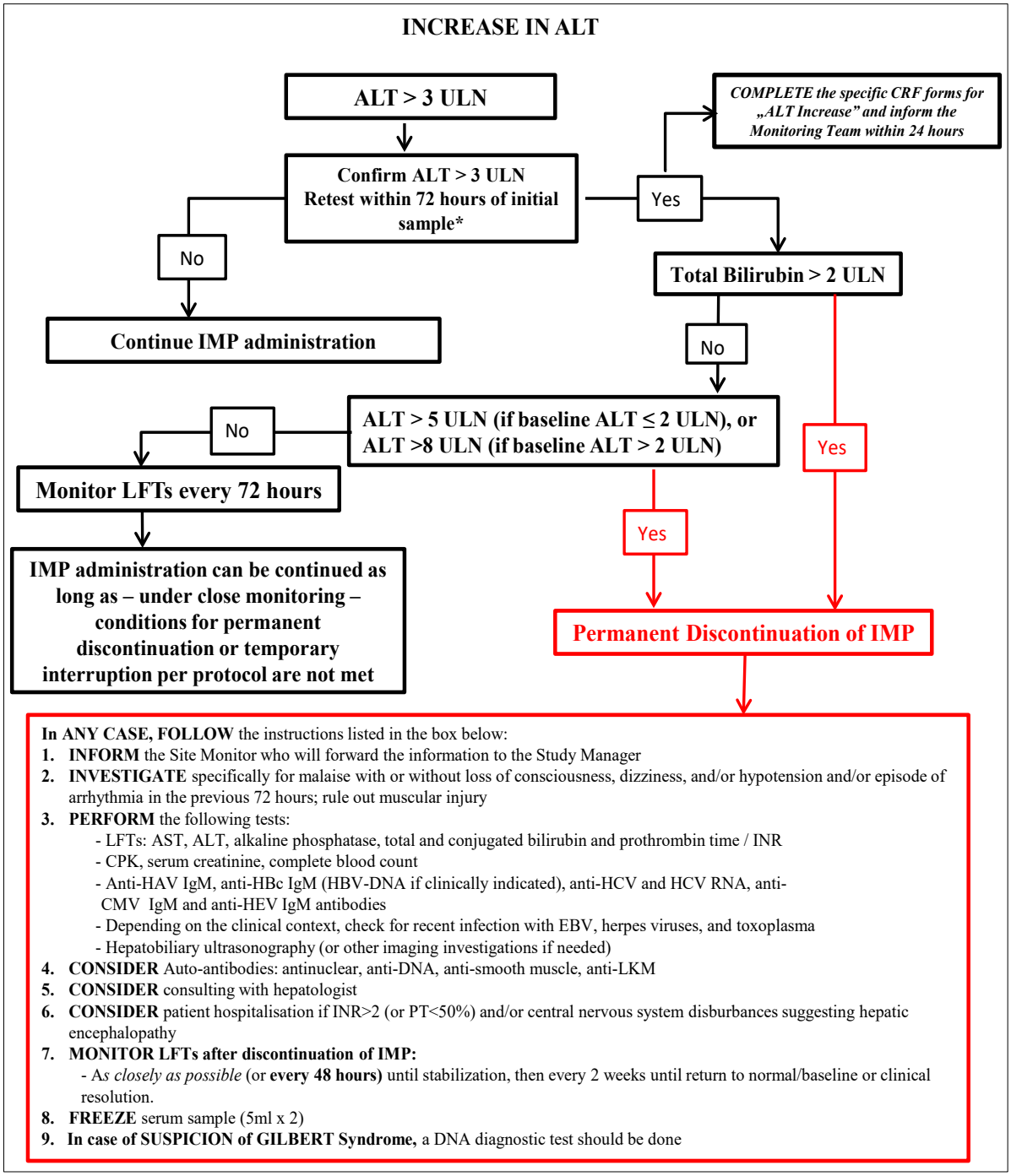
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or medical reasons resulting in an elective termination will be reported as an AE or SAE.

- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

- Any post-trial pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 13.5.4. While the investigator is not obligated to actively seek this information in former trial patients, they may learn of an SAE through spontaneous reporting.

- Any female patient who becomes pregnant while participating in the trial will be discontinued from study drug treatment.

13.7 Appendix: Liver Safety



Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CMV, cytomegalovirus; CPK, creatine phosphokinase; CRF, case report form; DNA, deoxyribonucleic acid; EBV, Epstein-Barr

virus; HAV, hepatitis A virus; HBc, hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; IgM, immunoglobulin M; IMP, investigational medicinal product; INR, international normalized ratio; LFT, liver function test; LKM, liver-kidney microsome; PT, prothrombin time; RNA, ribonucleic acid; ULN, upper limit of normal.

*If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.

Notes:

"Baseline" refers to ALT value at the baseline visit or, if the baseline value is unavailable, to the last ALT value before the baseline visit. The algorithm does not apply to instances of an increase in ALT during screening.

Section 13.5 provides guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value if the baseline value is >ULN.

13.8 Appendix: Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Definition of Source Data

Source Data to Be Found in the Patient's File

Evaluations that are reported in the eCRF must be supported by appropriately signed, related, and identified source documentation that may include, but is not limited to the following:

- Agreement and signature of ICFs (Section 9.3) with the trial identification and any privacy forms.
- Trial identification (name).
- Treatment kit number, dates of administration, and doses of study drug administered.
- Medical, surgical, and disease history, including information on the following:
    - Demography, inclusion and exclusion criteria.
    - History of alcohol consumption and smoking.
    - Comorbidities.
    - Last participation in a clinical trial.
    - Contraception method for WOCBP.
    - Previous and concomitant medications, including treatment for diabetes.
    - Dates and times of visits and assessments, including examination report.

- Vital signs, height, body weight, clinical safety laboratory reports.
- AEs and follow-up.

- If there is an SAE, the site should file in the source documents, at least, copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature trial discontinuation (if any) and reason.

Source documentation may be found in the following:

- Patient's identity (identification card or other verification document).
- Medical history.
- Nursing notes.
- Physician's notes.
- Patient's eDiary.
- Dated and signed print outs with SMPG downloaded from glucose meter.

Source Data Verification Requirements for Screen Failures

For screen failure patients, the following source data must be verified: patient's identification details, the informed consent signed by the patient, the trial identification (name), dates of trial visits, and the main reasons for screen failure.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.