



AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: SOLIQUA™ 100/33

A 26-week randomized, open-label, active-controlled, 2-treatment arm, parallel-group multi-center study, comparing the efficacy and safety of Soliqua™ 100/33 versus Lantus® in ethnically/racially diverse patients with Type 2 diabetes mellitus inadequately controlled on basal insulin and oral antidiabetic agents

STUDY NUMBER: LPS14860

STUDY NAME: LixiLan-D (DIVERSITY)

VERSION DATE / STATUS: Approval date (18-Dec-2017) / Approved

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CLINICAL TRIAL SUMMARY

COMPOUND: SOLIQUA 100/33	STUDY No.: LPS14860 STUDY NAME: LixiLan-D (Diversity)
TITLE	A 26-week randomized, open-label, active-controlled, 2-treatment arm, parallel-group multi-center study, comparing the efficacy and safety of Soliqua™ 100/33 versus Lantus® in ethnically/racially diverse patients with Type 2 diabetes mellitus inadequately controlled on basal insulin and oral antidiabetic agents
INVESTIGATOR/TRIAL LOCATION	United States: Multicenter
PHASE OF DEVELOPMENT	3b
STUDY OBJECTIVES	<p>Primary objective:</p> <ul style="list-style-type: none"> To demonstrate the superiority of Soliqua 100/33 versus Lantus in the hemoglobin A1c (HbA1c) change from baseline to Week 26 within the overall population To demonstrate the benefit of Soliqua 100/33 versus Lantus in the HbA1c change from baseline to Week 26 within each ethnic/racial subgroup evaluated (ie, Hispanics of any race, non-Hispanic black/African Americans and non-Hispanic Asians) <p>Secondary objectives:</p> <ul style="list-style-type: none"> To assess the effects of Soliqua 100/33 versus Lantus on the secondary efficacy parameters to Week 26 (see “Study Endpoints”) within each ethnic/racial subgroup evaluated To assess the change from baseline to Week 26 in daily insulin glargine dose within each ethnic/racial subgroup To evaluate the safety and tolerability (eg, gastrointestinal tolerability) of Soliqua 100/33 versus Lantus to Week 26 within each ethnic/racial subgroup <p>Other objectives:</p> <ul style="list-style-type: none"> To assess the effects of Soliqua 100/33 versus Lantus on the other efficacy parameters to Week 26 for the selected endpoints (see “Study Endpoints”) within each ethnic/racial subgroup evaluated To assess the effects of Soliqua 100/33 versus Lantus on efficacy and safety parameters to Week 26 in the overall population To evaluate and compare the effect of Soliqua 100/33 versus Lantus on Patient Reported Outcome (PRO) measures to Week 26 within each ethnic/racial subgroup
STUDY DESIGN	Open-label, 1:1 randomized, active-controlled, 26-week duration, parallel-group, multicenter, US-only, Phase 3b study to compare the efficacy and safety of Soliqua 100/33 to Lantus overall and in ethnically/racially diverse groups with Type 2 diabetes mellitus (T2DM) inadequately controlled on basal insulin and on 1 or 2 oral antidiabetic (OAD) agents. The patients will be randomized according to their self-reported ethnicity/race (ie, Hispanics of any race, non-Hispanic black/African Americans and non-Hispanic Asians); randomization will be capped to include an approximately similar numbers of patients (ie, 400) within each ethnic/racial subgroup, with approximately 200 patients per ethnic/racial group receiving Soliqua 100/33 and approximately 200 receiving Lantus. Additionally, to ensure a balanced investigational medicinal product (IMP) allocation,

	<p>randomization will be stratified by their self-reported ethnic/racial group, screening HbA1c value (<8.5% versus ≥8.5%), the background use of sodium-glucose co-transporter 2 (SGLT-2) inhibitors (yes/no) and the background use of sulfonylureas (SUs) (yes/no). Patients will participate in 1 of 2 ways, either at a traditional 'brick & mortar' investigational site, or fully remotely through a virtual (telemedicine) arrangement.</p> <p>The study will consist of 3 periods:</p> <ul style="list-style-type: none"> • An up to 2-week screening period • A 26-week open-label randomized treatment period: at the end of the screening period (Week 0, Visit 2) patients will be randomized to receive either Soliqua 100/33 or Lantus • A 3-day post-treatment safety follow-up period: patients will perform the safety follow-up visit 3 days after the Week 26 visit, except for those who prematurely and permanently discontinued IMP administration during the randomized treatment period, who should continue all study visits and assessments per protocol (except for the follow-up visit). <p>The maximum study duration per patient will be approximately 29 weeks.</p>
<p>STUDY POPULATION Main selection criteria</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients with T2DM diagnosed at least 1 year prior to the screening visit (signing of informed consent); • Uncontrolled diabetes as demonstrated by a screening centrally-measured HbA1c between 7.5% and 10% (inclusive); • Patients who are Hispanics of any race, non-Hispanic black/African Americans or non-Hispanic Asians; Note: Decision for ethnic/racial inclusion will be made based on the patient's self-identification. Mixed-race patients must select 1 of the above-mentioned categories. If such selection cannot be made, the candidate will be ineligible to participate in the study. • Patients who have been treated with any basal insulin (ie, glargine (100 U/mL or 300 U/mL), detemir, degludec, intermediate-acting [human NPH]) for at least 6 months prior to Visit 1; • The basal insulin regimen (ie, type of insulin and time/frequency of the injection) has been stable for at least 3 months prior to Visit 1; • The basal insulin dose has been stable (defined as up to ±20% [1/5 of the dose] variability) for at least 2 months prior to Visit 1 within the following dose ranges: <ul style="list-style-type: none"> - 15 to 50 units/day if HbA1c at Visit 1 is ≤8.5% and - 15 to 40 units/day if HbA1c at Visit 1 is >8.5% • Patients receiving 1 or 2 of the following oral antidiabetic (OAD) drugs: metformin, pioglitazone/rosiglitazone, an SGLT-2 inhibitor or a SU, at stable doses for at least 12 weeks prior to Visit 1; • Metformin dose must have been ≥1500 mg/day or the Maximum Tolerated Dose (MTD), according to the Investigator's judgment. • Sulfonylurea dose must be ≥ the half maximum approved dose according to the local label. For patients with an HbA1c <8%, the SU dose must be reduced by 50% starting with the day of initiation of IMP administration; subsequently, the dose can be up-titrated according to the Investigator's judgment up to the dose previously taken by the patient. Additional increases in SU dose (above baseline dose) should not be made unless the patient is rescued, according to the protocol rescue procedures.

	<ul style="list-style-type: none">• Patients willing and able to perform self-monitoring of plasma glucose (SMPG);• Signed written informed consent. <p>Exclusion criteria:</p> <ul style="list-style-type: none">• Age <18 years of age at Visit 1;• A body mass index (BMI) ≤ 20 or >40 kg/m² at Visit 1;• Fasting plasma glucose (FPG) >200 mg/dL (by central lab measurement) at Visit 1 (1-time repeat measurement before Visit 2 is permitted);• Type 1 diabetes mellitus or any diabetes other than T2DM;• Any use of OAD drugs other than those described in the inclusion criteria (eg, but not limited to, glucagon-like peptide-1 receptor agonist [GLP-1 RA], dipeptidyl peptidase 4 [DPP4] inhibitors) within 12 weeks prior Visit 1;• Use of any other type of insulin except for basal insulin (eg, prandial or premixed insulin, insulin pump) within 6 months prior to Visit 1; Note: History of short-term treatment (ie, ≤ 10 days) with other insulin types due to intercurrent illness is permitted at the discretion of the Investigator.• Known history of discontinuation of treatment with a GLP-1 receptor agonist due to safety/tolerability reasons;• Use of systemic glucocorticoids for a total duration of >7 days within 12 weeks prior to Visit 1;• Initiation/change in type or dose of a weight loss drug within 12 weeks prior to Visit 1;• Use of an investigational drug within 1 month or 5 times the duration of the pharmacodynamic effect, whichever is longer, prior to Visit 1;• History of metabolic acidosis, including diabetic ketoacidosis within 12 months prior to Visit 1;• History of stroke, myocardial infarction, unstable angina or heart failure requiring hospitalization within 6 months prior to Visit 1; planned hospitalization for any reason during the duration of the study;• Known history of drug or alcohol abuse within 6 months prior to Visit 1;• Clinically significant laboratory findings at Visit 1, including:<ul style="list-style-type: none">- Amylase and/or lipase >3 times the upper limit of the normal (ULN) laboratory range- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times ULN- Positive serum pregnancy test;• Contraindication to Soliqua 100/33 or Lantus use, according to local label;• History of hypersensitivity to insulin glargine or lixisenatide, or to any of the excipients;• Contraindications to the specific background OADs that each individual patient is taking (as applicable), according to the local label;• An estimated glomerular filtration rate <30 mL/min/1.73m² (more stringent renal function restrictions, depending on the patient's background OAD use are to be applied, according to the local label and the Investigator's judgment);
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	<ul style="list-style-type: none"> • History of pancreatitis (unless pancreatitis was related to gallstones and cholecystectomy was already performed), chronic pancreatitis, pancreatitis during a previous treatment with incretin therapies, pancreatectomy, stomach/gastric surgery; • Known history or presence of clinically-significant gastroparesis; • Pregnancy or lactation; women of childbearing potential not protected by highly-effective contraceptive methods (as defined in the Informed Consent) and/or who are unwilling or unable to be tested for pregnancy; planning pregnancy during the duration of the study; • Conditions/situations such as: <ul style="list-style-type: none"> - Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint (eg, sickle cell anemia, hemoglobinopathy or hemolytic anemia, severe anemia [screening Hgb <8.0 g/dL; transfusion indicated], receipt of blood or plasma products within 12 weeks of Visit 1), - Patients with conditions/concomitant diseases precluding their safe participation in this study (eg, active malignant tumor, clinically-significant psychiatric disorders, major systemic diseases, presence of clinically significant diabetic retinopathy or presence of macular edema likely to require treatment within the study period), - Impossibility to meet specific protocol requirements (eg, scheduled visits, patients unable to fully understand patient's study documents and to complete them), - Uncooperative patient or any condition that could make the patient potentially non-compliant to the study procedures (eg, patient unable or unwilling to do self-injections or blood glucose monitoring using the sponsor-provided blood glucose meter at home, etc), • Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
<p>Total expected number of patients</p> <p>Expected number of sites</p>	<p>A sufficient number of patients will be screened to ensure randomization of approximately 1200 patients (approximately 600 in each treatment arm) with an approximately similar number of patients (ie, 400) within each ethnic/racial group (approximately 200 per group/treatment arm).</p> <p>A sufficient number of sites including traditional brick and mortar and/or virtual (telemedicine) sites within the United States will be employed.</p>
<p>STUDY TREATMENTS</p> <p>Investigational medicinal products formulation</p>	<p>Tested drug:</p> <p>Soliqua 100/33 (insulin glargine/lixisenatide fixed ratio combination) is supplied for subcutaneous (SC) injection as a sterile aqueous solution in a 3:1 ratio SoloStar® pen-injector. The prefilled disposable pen-injector contains 3 ml of sterile solution of 100 U/mL insulin glargine and 33 µg/mL lixisenatide in a ratio of 3 units (U) of insulin glargine to 1 µg lixisenatide and it allows administration of daily combination doses between 15 U/5 µg and 60 U/20 µg. The dose of the combination is titrated according to the patient's need for insulin. Only the insulin glargine dose appears in the device dosing window; the lixisenatide dose does not appear in the dose window although lixisenatide is premixed in the cartridge. The lixisenatide dose is increased or decreased concomitantly with insulin glargine dose change.</p>

	<p>Control drug:</p> <p>Lantus (insulin glargine) is being supplied for SC injection as a sterile aqueous solution in a prefilled (disposable) Lantus SoloStar pen-injector containing a 3 mL solution of insulin glargine 100 U/mL. The disposable SoloStar pen-injector allows for a dose setting in the range of 1-80 U with a minimum dose increment of 1 U.</p> <p>Mixing of Soliqua 100/33 and Lantus with other insulins or dilution of the test drug is not permitted.</p>
<p>Route(s) of administration:</p>	<p>Subcutaneous injection</p>
<p>Dose regimen:</p>	<p>Injection time:</p> <p>Soliqua 100/33 should be self-administered once daily in the morning within 1 hour (0 to 60 minutes) before breakfast.</p> <p>Lantus should be self-administered once daily at any time of the day but at about the same time every day. The injection time will be determined at the discretion of the patient and Investigator at the time of randomization and it should remain about the same (± 120 minutes) until the end of the randomized treatment period.</p> <p>The first dose of IMP will be administered on the day of randomization (Day 1), either at the site (Soliqua 100/33 and Lantus on a morning (AM) dosing regimen) or outside the site location (Lantus administered on a regimen other than morning [PM]). If, due to logistical reasons, administration of IMP on the day of randomization is not possible, administration within the 3 days following randomization is permitted.</p> <p>Starting Dose:</p> <p>Soliqua 100/33</p> <ul style="list-style-type: none"> • Patients on a background basal insulin dose <30 U/day (at the time of randomization): starting dose should be 15 U of insulin glargine (corresponding to 5 μg lixisenatide) • Patients on a background basal insulin dose ≥ 30 U/day (at the time of randomization): starting dose should be 30 U of insulin glargine (corresponding to 10 μg lixisenatide) <p>Lantus: The initial dose will be the same as the background basal insulin dose at which the patient is randomized unless transitioning from U300 insulin glargine, insulin administered twice daily or insulin detemir, when a 20% (1/5) reduction in dose is required to initiate Lantus.</p> <p>Note: The 20% dose reduction recommendation for Lantus does not apply to Soliqua 100/33.</p> <p>Dose Adjustments:</p> <p>The same dose adjustment algorithm is recommended for Soliqua 100/33 and Lantus. The insulin doses will be up-titrated by 2 U or a maximum of 4 U/week (see algorithm in the table below), until the patient reaches a target fasting SMPG of 80 to 100 mg/dL (4.4 to 5.6 mmol/L), inclusive, without clinically significant hypoglycemia episodes.</p> <p>Good clinical judgment should be exercised when titrating the basal insulin dose. Study patients should be trained and retrained on an ongoing basis to ensure proper understanding of titration procedures and a very close communication between the patient and the study site will be required to ensure adequate titration with minimization of associated risks.</p>

	<p>Week 12. Once the target SMPG has been achieved and until the end of the study, the basal insulin dose will be adjusted as necessary to maintain this fasting SMPG target according to the dose adjustment guidelines in Section 8.1.1.</p> <p>Recommended dose changes are to be based on a median of fasting SMPG values from the last 3 days (including the day of titration) measured by the patient using glucometers and accessories supplied by the Sponsor.</p> <table border="1" data-bbox="715 497 1452 913"> <thead> <tr> <th data-bbox="715 497 1139 573">Median of fasting SMPG values from last 3 days</th> <th data-bbox="1139 497 1452 573">Insulin glargine dose adjustments (U/day)</th> </tr> </thead> <tbody> <tr> <td data-bbox="715 573 1139 618">>140 mg/dL (>7.8 mmol/L)</td> <td data-bbox="1139 573 1452 618">+ 4</td> </tr> <tr> <td data-bbox="715 618 1139 663">>100 and ≤140 mg/dL (>5.6 and</td> <td data-bbox="1139 618 1452 663">+ 2</td> </tr> <tr> <td data-bbox="715 663 1139 734">Glycemic target: >80 and ≤100 mg/dL (>4.4 and ≤5.6 mmol/L), inclusive</td> <td data-bbox="1139 663 1452 734">No change</td> </tr> <tr> <td data-bbox="715 734 1139 801">≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)</td> <td data-bbox="1139 734 1452 801">-2</td> </tr> <tr> <td data-bbox="715 801 1139 913"><60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or 1 severe hypoglycemia.</td> <td data-bbox="1139 801 1452 913">-2 to -4 or at the discretion of the Investigator or medically qualified designee</td> </tr> </tbody> </table> <p>Notes: A titration dose increase of 2 or 4 U for Soliqua 100/33 or Lantus may be split into 2 incremental dose steps, rather than implementing the entire dose increase at one time, if it is considered by the Investigator or medically-qualified designee to be in the best interest of the patient.</p>	Median of fasting SMPG values from last 3 days	Insulin glargine dose adjustments (U/day)	>140 mg/dL (>7.8 mmol/L)	+ 4	>100 and ≤140 mg/dL (>5.6 and	+ 2	Glycemic target: >80 and ≤100 mg/dL (>4.4 and ≤5.6 mmol/L), inclusive	No change	≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)	-2	<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or 1 severe hypoglycemia.	-2 to -4 or at the discretion of the Investigator or medically qualified designee
Median of fasting SMPG values from last 3 days	Insulin glargine dose adjustments (U/day)												
>140 mg/dL (>7.8 mmol/L)	+ 4												
>100 and ≤140 mg/dL (>5.6 and	+ 2												
Glycemic target: >80 and ≤100 mg/dL (>4.4 and ≤5.6 mmol/L), inclusive	No change												
≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)	-2												
<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or 1 severe hypoglycemia.	-2 to -4 or at the discretion of the Investigator or medically qualified designee												
<p>Non-investigational medicinal products</p> <p>Background OAD Therapy</p> <p>Route(s) of administration:</p> <p>Dose regimen:</p>	<p>Background OAD agents and rescue therapy will be considered as non-investigational medicinal products (NIMPs).</p> <p>Oral</p> <p>The type and dose of OAD (except rescue treatment or adjustment of the SU dose as per protocol) received by the patient at the time of Visit 1 will not be modified until the end of the study unless there is a specific safety issue/medical need related to this treatment.</p>												
<p>Rescue Therapy</p>	<p>A rescue treatment is to be initiated, according to the Investigator's judgment in the event that at (or after) Week 12, the HbA1c is >8%.</p> <p>AND IF:</p> <p>No explanation can be found for the insufficient glucose control (eg, infectious disease, lack of compliance with study treatment, non-compliance with diet and lifestyle requirements)</p> <p>The appropriate actions to correct potential triggering factors fail</p> <p>For patients randomized to Soliqua 100/33, an insulin glargine dose >60 units/day is necessary to decrease HbA1c below the threshold values (ie, further dose titration is not possible) and</p> <p>The HbA1c value exceeding the threshold is confirmed by repeat test (performed at the central laboratory) approximately 4 weeks after the initial measurement (or at a time point considered appropriate by the Investigator)</p> <p>Note: The 4-week HbA1c repeat may be waived if, according to the Investigator's judgment, the patient does not have any precipitating factors leading to an elevated HbA1c that must be addressed and it is in the best</p>												

	<p>interest of the patient to initiate rescue therapy immediately.</p> <p>Rapid acting insulin (glulisine) is suggested to be utilized as rescue therapy and it should be started as a once-daily regimen administered prior to the main meal of the day (excluding breakfast). If, according to the Investigator's judgment, rapid-acting insulin is not in the best interest of the patient, addition of an OAD (within the category of permitted background medications) or increases in the OAD doses already taken by the patient (according to the local label) may be considered as a secondary option for rescue therapy.</p> <p>Note: GLP-1 receptor agonists are not permitted as rescue therapy.</p> <p>All assessments planned for the 26-week end-of-treatment visit are to be performed before initiating rescue therapy.</p> <p>After these assessments are completed and rescue therapy is initiated, the patient should remain in the study and continue to administer the study treatment (including background therapy). The planned visits and assessments should be performed until the last scheduled visit.</p>
<p>ENDPOINTS</p>	<p>Primary endpoint</p> <ul style="list-style-type: none"> • Change from baseline to Week 26 in HbA1c (%) <p>Secondary endpoints:</p> <p>Efficacy</p> <ul style="list-style-type: none"> • Percentage (%) of patients achieving the HbA1c target of <7% at Week 26 • Change in 2-hour postprandial glucose (PPG) as measured utilizing a standardized meal test at Week 26 (for patients that performed the standardized meal test) • Change in 2-hour glycemic excursions as measured utilizing a standardized meal test at Week 26 (for patients that performed the standardized meal test) • Change from baseline to Week 26 in daily insulin glargine dose • Change from baseline to Week 26 in body weight <p>Safety</p> <ul style="list-style-type: none"> • Hypoglycemia <ul style="list-style-type: none"> - Documented hypoglycemia (plasma glucose values ≤ 70 mg/dL [3.9 mmol/L]) - Symptomatic hypoglycemia - Documented hypoglycemia (plasma glucose values < 54 mg/dL [3.0 mmol/L]) - Symptomatic hypoglycemia - Severe hypoglycemia • Adverse events (AEs), including gastrointestinal AEs • Serious adverse events (SAEs) • Adverse events of special interest (AESI): serious allergic/hypersensitivity reactions, pregnancy, ALT>3 x ULN, symptomatic overdose of IMP/NIMP • Vital sign parameters (change from baseline) <p>Other efficacy endpoints:</p> <ul style="list-style-type: none"> • HbA1c change from baseline to Week 12 • Fasting plasma glucose change from baseline to Week 26 • Percent of patients requiring rescue therapy by Week 26 • Percentage of patients reaching the HbA1c target of <7% at Week 26 with no body weight gain

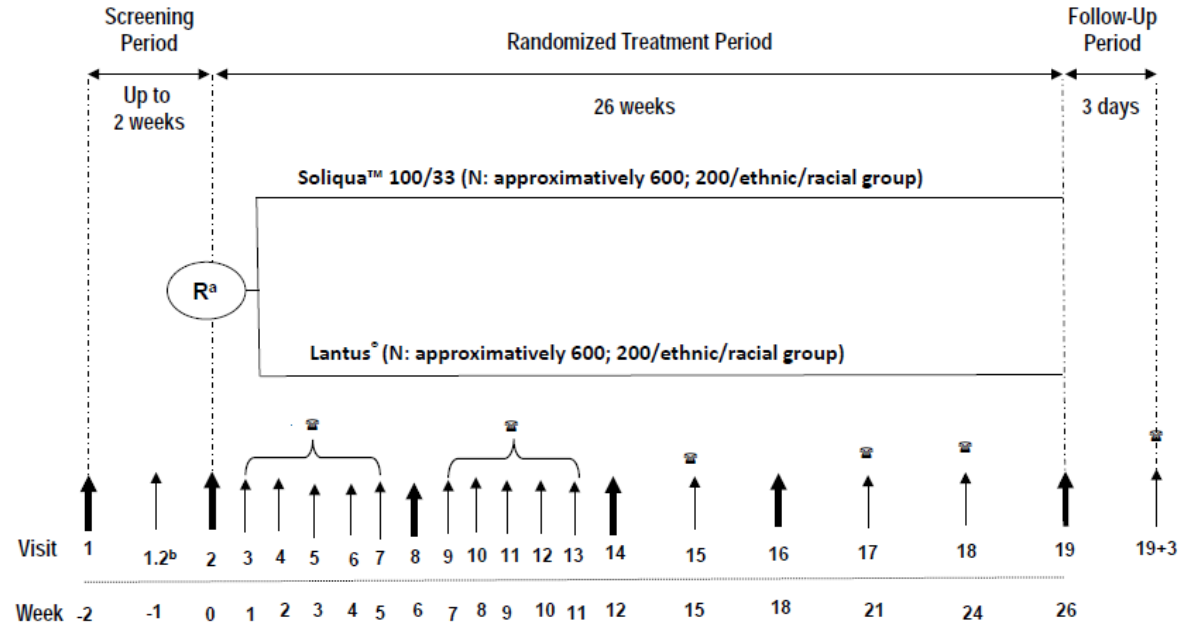
	<ul style="list-style-type: none"> • Percentage of patients reaching the HbA1c target of <7% at Week 26 with no documented symptomatic hypoglycemia (SMPG ≤70 mg/dL [3.9 mmol/L]) • Percentage of patients reaching the HbA1c target of <7% at Week 26 with no documented symptomatic hypoglycemia (SMPG <54 mg/dL [3.0 mmol/L]) • Percentage of patients reaching the HbA1c target of <7% at Week 26 with no body weight gain and no documented symptomatic hypoglycemia (SMPG ≤70 mg/dL [3.9 mmol/L]) • Percentage of patients reaching the HbA1c target of <7% at Week 26 with no body weight gain and no documented symptomatic hypoglycemia (SMPG <54 mg/dL [3.0 mmol/L]) • Patient Reported Outcome measures: <ul style="list-style-type: none"> - Treatment Related Impact Measure – Diabetes (TRIM-D) - Patient and Physician Global Treatment Effectiveness Evaluation Scales
<p>ASSESSMENT SCHEDULE</p>	<p>Visit schedule: The schedule of study-related procedures/assessments is detailed in the Study Flow Chart (Table 1).</p> <p>Early termination: Patients who prematurely and permanently discontinue IMP administration for any reason should have a visit as soon as possible for the assessments normally planned for the last dosing day with the IMP, ie, Week 26. Afterward, these patients should continue in the study up to their scheduled date of study completion. They should be followed up according to the study procedures as specified in the protocol (except for the 3-day safety follow-up visit).</p>
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample size determination: Based on clinical trial data, along with additional modeling exercises (to evaluate the impact of the differences in study design between this study and the preapproval studies, eg, lack of placebo run-in), assuming a true difference of 0.4% for HbA1c change, and a standard deviation of 0.95%, 200 patients per ethnic/racial subgroup would provide 96% power for superiority of iGlarLixi to iGlar in an individual ethnic/racial subgroup at the 1-sided 0.025/3 significance level. This would also provide 90% power for superiority in all 3 subgroups. In order to ensure an overall family-wise 2-sided error rate of 0.05, a Hommel procedure will be used. Calculations were made using nQuery Advisor 7.0. A total sample size of 1200 patients for inclusion in the intent-to-treat (ITT) population is planned.</p> <p>Analysis population: Efficacy analyses will be based on the ITT population, defined as all randomized patients. Patients will be analyzed for efficacy analyses according to the treatment group to which they are randomized. Safety data will be summarized using the Safety Population, defined as all randomized patients who actually received at least 1 dose of IMP, analyzed according to the treatment actually received.</p>

	<p>Primary analysis:</p> <p>Analyses of the primary efficacy endpoint (change from baseline to Week 26 in HbA1c) will be performed using the ITT population, using HbA1c values obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or rescue medication use.</p> <p>The baseline value is defined as the last available value prior to the first dose administration of investigational medicinal product or the last available value on or before the date of randomization if not treated with open-label IMP.</p> <p>The change in HbA1c from baseline to Week 26 (primary endpoint) will be analyzed with missing values imputed by control-based jump to reference multiple imputation method. This approach assumes missing at random mechanism for missing data in the Lantus (control) group. However, it does not assume such a missing at random mechanism for missing data in the Soliqua 100/33 group. For a patient in the Soliqua 100/33 group, it assumes that the patient will lose the Soliqua 100/33 treatment benefit and uses the parameters of the Lantus (control) group to calculate the patient's post-dropout mean response for the conditional mean in the imputation model.</p> <p>Each of the completed datasets will be analyzed by the analysis of covariance (ANCOVA) model with treatment groups, randomization strata of ethnicity/race, SGLT-2 use (Yes, No), and SU use (Yes, No), as fixed effects, and baseline HbA1c as the covariate. Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from baseline to Week 26 for each treatment group, as well as the between-group difference. If the upper bound of the 2-sided 95% CI for the adjusted mean difference (Soliqua 100/33 vs. Lantus) in HbA1c change from baseline to Week 26 is <0, then superiority of Soliqua 100/33 will be declared.</p> <p>Analysis of secondary and other endpoints:</p> <p>Analysis of secondary and other endpoints will be done utilizing the data obtained up to Week 26 during the randomized treatment period.</p> <p>All categorical secondary efficacy endpoints including the proportion of patients reaching HbA1c targets will be analysed using a logistic regression model adjusting for treatment and appropriate baseline covariates. Summaries and appropriate inferential analyses will be provided for all continuous secondary efficacy endpoints.</p> <p>Summaries will be prepared for safety and tolerability findings and PRO measures.</p> <p>To control the Type I error, a Hommel testing procedure will be applied for the primary endpoint. For the primary analysis (change from baseline to Week 26 in HbA1c), no multiplicity adjustment is needed to control the Type I error in the overall population since only 1 comparison of Soliqua 100/33 versus Lantus will be performed. Once it passes statistical significance at the 2.5% level (1-sided), the Hommel procedure will be utilized for testing the primary endpoint in each ethnic/racial group. If the largest p-value from the 3 ethnic/racial groups is less than or equal to 0.05 then statistical significance is achieved at all 3 ethnic/racial groups; if the largest p-value is greater than 0.05 but the second-largest p-value is less than or equal to 0.025 then statistical significance is achieved for the 2 ethnic/racial groups corresponding to the 2 smaller p-values; if the second-largest p-value is greater than 0.025 and the smallest p-value is less than or equal to 0.0167 OR the smallest p-value is less than or equal to 0.025 and</p>
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	<p>the second-smallest p-value is between 0.025 (exclusive) and 0.0333 (inclusive), then statistical significance is only achieved for the ethnic/racial group corresponding to the smallest p-value. This procedure has statistical validity since the testing is among different and independent subgroups of patients.</p> <p>Details of any testing procedure for key secondary endpoints to control the Type 1 error will be described in the study protocol.</p>
DURATION OF STUDY PERIOD (per patient)	A maximum of 29 weeks per patient.
STUDY COMMITTEES	<p>Steering Committee: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Data monitoring committee: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Adjudication committee: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



R = Randomization; patients will continue their background OADs at stable doses throughout the study; background basal insulin will be stopped and replaced with the IMP.

a: Stratified by: (1) ethnicity/race (capped, to allow enrollment of comparable number of patients within each ethnic group), (2) HbA1c at Visit 1, (3) background use of SGLT2 inhibitors and (4) background SU use.

b: A sub-set of patients only.

☎ = Remote visit (telephone or videoconference) for all sites ↑ = On-site (in person) visit for brick-and-mortar sites/ remote visit (telephone or videoconference) for fully-remote sites

1.2 STUDY FLOW CHART

Table 1 - Screening and randomized treatment period flow chart

Study Period	Screening		Open-label Randomized Treatment																	Follow-Up Visit	
	1	1.2 ^b	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 ^c	19 + 3
VISIT ^a																					
WEEK	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	26	26+3 days
Inclusion criteria including Informed Consent ^d	x		x																		
Exclusion criteria	x		x																		
Patient demography	x																				
Medical/surgical history (including diabetes)	x																				
Prior medication history	x	x																			
Physical examination	x																				
Height	x																				
Body weight and BMI ^e	x		x												x		x				x
Vital signs ^f	x		x						x						x		x				x
Diet and lifestyle counseling ^g	x		x						x						x		x				x
IRT contact ^h	x		x						x						x		x				x
Randomization			x																		
Dispensation of IMP (as appropriate)			x						x						x		x				
Pen-injector and self-injection training and re-training ⁱ			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Review and evaluation/adjustment of IMP doses			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Study Period	Screening		Open-label Randomized Treatment																	Follow-Up Visit		
	1	1.2 ^b	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 ^c	19 + 3	
VISIT ^a				☎	☎	☎	☎	☎		☎	☎	☎	☎	☎		☎		☎	☎		☎	
WEEK	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	26	26+3 days	
Collection of used and unused IMP pens; compliance check									x						x		x				x	
Glucometer/supplies/diary dispensation			x																			
Glucometers, SMPG, hypoglycemia, insulin dose titration, diary training and re-training ⁱ			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
SMPG ^j			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Two-hour standardized meal test (a sub-set of patients only)		x																			x	
HbA1c (central laboratory)	x														x		x				x	
FPG (central laboratory) (A 1-time repeat measurement before Visit 2 is permitted)	x														x						x	
PRO questionnaires ^k			x												x						x	
Hematology ^l	x																					
Serum chemistry ^m	x																					
Urinalysis ⁿ	x																					
eGFR ^o	x																					
Amylase, Lipase	x																					
Serum calcitonin			x																			
Pregnancy test ^p	x		x												x		x				x	
Concomitant medications	Continuously assessed and recorded throughout the study																					
AEs/SAEs/AESIs/hypoglycemia collection	Continuously assessed and recorded throughout the study																					

☎ = Remote visit (telephone or videoconference); all other visits will be performed in person, at the site location, except for the patients that will be enrolled through the virtual site model, who will complete all study visits in a remote setting (as described in [Section 10](#)).

- a. Screening period duration is of up to 2 weeks (ie, it can be less than 2 weeks if all required procedures have been performed and patient's eligibility has been confirmed). Starting with Visit 3 through (and including) Visit 14, a ± 2 -day window, calculated relative to the Randomization Visit (Visit 2) is permitted; for Visits 15 through 18, a ± 3 -day window is permitted, while for Visit 19 a $+3$ -day window is permitted. If a study visit is performed outside of the permitted window, the subsequent visits must be scheduled according to the original schedule (ie, relative to the date of Visit 2, Randomization Visit). The date of the follow-up visit must be determined relative to the date of Visit 19. Additional remote visits should be scheduled as often as deemed necessary by the Investigator.
- b. Mandatory for all patients until at least 75 randomized patients per treatment/ethnicity/race group completed the test during the screening period; the visit can be performed any time prior to Visit 2, once the patient's eligibility based on Visit 1 criteria has been confirmed. Sponsor or designee will communicate when/if this evaluation is no longer required for study patients.
- c. In case of rescue therapy initiation or if IMP is being permanently discontinued, Week 26 (Visit 19) procedures should be performed before starting rescue therapy/IMP discontinuation; subsequently, patients should continue study treatment and all visits/procedures should be performed per protocol.
- d. Informed consent should be collected at Visit 1 only, before any other study procedures are performed (or when amendments to the consent are created by the Sponsor or designee).
- e. BMI will be calculated by the site at Visit 1 only using the following formula: $BMI = \text{weight (kg)} / (\text{height in m})^2$.
- f. Blood pressure and heart rate will be measured after 5 minutes rest in seated position.
- g. Additional counseling will be performed as appropriate throughout the study.
- h. IRT will be contacted by the site at the pre-specified timepoints, as well as any other time when the patient needs re-dispensation of the IMP.
- i. Repeated as often as necessary, including during remote visits.
- j. SMPG monitoring is to be performed to guide insulin titration and for hypoglycemia evaluation, as appropriate, by study patients after Visit 2 and throughout the study duration
 1. Fasting (prebreakfast/preinjection) SMPG should be performed daily until the FPG target has been achieved. Thereafter, the number of fasting SMPG measurements could be reduced, according to the Investigator's judgment, however at least 3 fasting SMPG measurements per week must be done.

Note: After randomization the fasting SMPG will follow the window for the preinjection SMPG
 2. Preinjection SMPG (within 30 minutes prior to the injection of Soliqua 100/33 or Lantus - if the latter is administered in the morning) during the randomized treatment period.
- k. PROs will be assessed per the following schedule:
 1. TRIM-D – to be done at Baseline, W12 and W26
 2. Patient/Physician assessments: W26.
- l. Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes and platelets.
- m. Serum chemistry: AST, ALT, ALP, total bilirubin (if $>ULN$, then the direct and indirect sub-fractions must be measured), creatinine, uric acid, sodium, potassium
- n. Urinalysis: pH, glucose, ketones, leukocytes, blood/hemoglobin, protein.
- o. Using the Modification of Diet in Renal Disease (MDRD) equation.
- p. Women of childbearing potential only; serum pregnancy test at Visit 1; urine pregnancy test at all subsequent visits for patients at traditional sites (if needed, a confirmatory serum pregnancy test can be performed). Investigators may conduct additional locally analyzed urine pregnancy tests as per their judgment. For patients participating at the designated site for the virtual study model, all pregnancy tests will be serum and for Visit 2, this may be done up to 1 week prior to the Visit 2 date (ie, it may be done at Visit 1.2, if patient performs this visit; the results must be obtained prior to patient randomization).

AE=adverse event; AL=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; eGFR=estimated glomerular filtration rate; FP=fasting plasma glucose; HbA1c =hemoglobin A1c; IMP=investigational medicinal product; IRT=interactive response technology; PRO=patient reported outcome; SAE=serious adverse event; SMPG=self-monitoring of plasma glucose; ULN=upper limit of normal.

☎ = Remote visit (telephone or videoconference); all other visits will be performed in person, at the site location, except for the patients that will be enrolled through the virtual (telemedicine) site model, who will complete all study visits in a remote setting.

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3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
BMI:	body mass index
CDC:	Center for Disease Control
CDE:	certified diabetes educator
CV:	curriculum vitae
DPP4:	dipeptidyl peptidase 4
eCRF:	electronic case report form
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
GLP-1 RA:	glucagon-like peptide-1 receptor agonist
HbA1c:	hemoglobin A1c
HLGT:	high level group term
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
MTD:	Maximum Tolerated Dose
NIMP:	non-investigational medicinal product
OAD:	oral antidiabetic, oral anti-diabetic
PCSA:	potentially clinically significant abnormality
PPG:	postprandial glucose
PRO:	patient-reported outcomes
PT:	preferred term
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SC:	subcutaneous
SD:	standard deviation
SGLT-2:	sodium-glucose co-transporter 2
SMPG:	self-monitoring of plasma glucose
SU:	sulfonylurea
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent AE
TRIM-D:	Treatment Related Impact Measure - Diabetes
U.S.:	United States
ULN:	upper limit of normal
USPI:	United States package insert
WOCBP:	women of childbearing potential

4 INTRODUCTION AND RATIONALE

As of 23 February 2017, the United States (U.S.) has a total resident population of 324 590 124, making it the third most populous country in the world (1). This population is characterized by significant ethnic and racial diversity, with 6 races (including the option for multiple races) being officially recognized by the U.S. Census Bureau as of 2000 (2).

According to the 2010 Census data, significant shifts have occurred in the ethnic and racial distribution of the U.S. population during the interval between 2000 and 2010, with increases in the percentage of minority groups. Specifically, the percentage of individuals identified as whites “alone” (ie, not reporting multiple races) decreased from 75% in 2000 to 72% in 2010; within this category, the percentage of non-Hispanic whites decreased from 69.1% in 2000 to 63.7% in 2010 (3). During the same decade, the overall Hispanic or Latino population increased from 12.5% to 16.3%, with noted variability among populations of different Hispanic origins (4); the black or African American population (alone or in combination) increased from 12.9% to 13.6% (5) and the U.S. Asian population increased from 4.2% to 5.6% (6). Consistently, the U.S. population projections developed by Pew Research Center as of February 2008 suggest that, by 2050, the non-Hispanic white population will represent 47% of the total U.S. population, while Hispanics or Latinos will make up 29% of the total population, non-Hispanic blacks 13%, and non-Hispanic Asians 9% (7).

Diabetes is a major cause of morbidity and mortality in the U.S. At the beginning of the millennium there were 15 million adults living with diabetes, with ethnic/racial minority populations bearing a disproportionate burden of the diabetes epidemic. The Behavioral Risk Factor Surveillance System reported in 2000 that 7% of Americans have diabetes, with prevalence rates of 7% among non-Hispanic whites, compared to 9% among Hispanics and 11% among African Americans (8). Furthermore, The Center for Disease Control (CDC) has reported that between 2010 and 2012, 29.1 million people (9.3% of U.S. population) had diabetes with Type 2 diabetes mellitus (T2DM) accounting for 90% to 95% of the cases in adults; the prevalence was 7.6% for non-Hispanic whites aged 20 years or older, 9% for Asian Americans, 12.8% for Hispanics, 13.2% for non-Hispanic blacks, and 15.9% for American Indians/Alaskan Natives of the same age (9). In addition to the differences in prevalence rates, higher rates of complications and worse control of diabetes are known to exist within the minority populations (8). These disparities are often the result of genetic variants but socioeconomic and lifestyle factors also influence outcomes (10).

Ethnic/racial differences in the pathogenesis and evolution of diabetes have been noted. For example, intensive treatment of African Americans with newly diagnosed diabetes can lead to remission of diabetes in 30% to 40% of patients (11, 12) while African Americans exhibit lower glucagon-like peptide-1 concentrations and increased inflammatory responses which may act synergistically to enhance the predisposition of obese African Americans to T2DM (13). Hispanic individuals are less likely to achieve glycemic goals during treatment, when compared to non-Hispanic whites and non-Hispanic blacks (14) and it is hypothesized that there is more rapid gastric occurring in these patients, leading to an increase in postprandial glucose and insulin resistance (15). T2DM in East Asians is characterized by beta cell dysfunction rather than insulin resistance. Also, meta-analyses suggest that incretin agents are more efficacious in Asian populations (16).

Considering the current and projected demographic shifts within the U.S. population as detailed above, as well as the disparities in the burden of diabetes and its complications/comorbidities among various ethnic/racial groups, it becomes critical to demonstrate that the efficacy and safety profile of medications is similar among these groups and/or to identify and address any significant differences, if applicable. However, as stated in the U.S. Food and Drug Administration (FDA) April 2013 Consumer Health Information Sheet (17), historically minorities and women have been under-represented in clinical trials and there is a paucity of randomized controlled trials that specifically investigate pharmacological treatment in minority populations. For example, according to a 2011 report from the conference “Dialogues on Diversifying Clinical Trials,” sponsored by FDA’s Office of Women’s Health and the Society for Women’s Health Research and supported by the Office of Minority Health:

- African Americans represent 12% of the U.S. population but only 5% of clinical trial participants;
- Hispanics make up 16% of the population but only 1% of clinical trial participants; and
- Men make up more than 2/3 of participants in clinical tests of cardiovascular (heart and blood vessel) devices.

The lack of minority population participation in clinical trials has previously been documented (18). This was also confirmed by a Sanofi internal comprehensive literature search (ie, review of PubMed clinical trial results from 1995 to 2015 on glucose-lowering agents in African American and Hispanic populations), which has shown that clinical trials in these 2 ethnic/racial groups are limited to “older” diabetes drugs (ie, metformin, sulfonylurea, rosiglitazone, and linagliptin). Similar findings were noted in a 2015 article by Ferdinand et al. (19) in which the objective was to evaluate the prevalence of diabetes and disease-related comorbidities as well as the primary endpoints of clinical studies assessing glucose-lowering treatments in African Americans, Hispanics, and Asians. Overall, the majority of publications that fit the search criteria pertained to native Asian patient populations (ie, Asian patients in Asian countries). Sulfonylureas, glucosidase inhibitors, miglitol, metformin, and rosiglitazone have been evaluated in African American and Hispanic populations, as well as in Asians. The literature on other glucose-lowering drugs in non-white races/ethnicities was found to be more limited (20).

Consistent with these general trends, during the clinical development of Soliqua 100/33, minority populations were not significantly represented in the pivotal trials, with Study EFC12404 enrolling 7% African American, 19% Hispanic and 2% Asian patients and Study EFC12405 enrolling 5% African American, 18% Hispanic, and 3% Asian patients.

Considering that racial health disparities are often influenced by lack of access to both quality healthcare as well as appropriate health awareness, this directly influences the lack of minority clinical trial populations. Consequently, it is our intention to conduct a diversity trial for Soliqua 100/33 employing many of the strategies that have been documented to recruit Hispanic, African American, and other minority populations. These strategies include recruiting minority Investigators to undertake this research, building a communication platform that is culturally sensitive and transparent in terms of the benefits and risks of the research, and to engage in an awareness campaign in the appropriate locations with respect to diabetes education, race/ethnicity

based differences in disease prevalence and symptoms and finally, the opportunity and mechanism by which to become involved in this important research.

Additionally, to expand access to the trial, a proportion of the participants enrolled may take part via a distributed clinical trial model. This includes operationalizing the trial by utilizing virtual electronic consent, telemedicine encounters using video-conferencing, and shipment of Investigational Medicinal Product (IMP) direct to patient to conduct trial activities that allow patients to take part in the trial who would otherwise be unable or unwilling to travel to a traditional study site (details to be documented in the appropriate virtual-site model Project Plan). The use of technologies to augment or replace traditional face-to-face interactions has become an important component of medical practice in many communities. Telemedicine is an important technology and its use is rapidly increasing. While telemedicine is a relatively new care-delivery model, it is not a departure from standard medical practice; in particular, the California Medical Board describes it as a “tool in medical practice, not a separate form of medicine.” Providers using telemedicine are held to the same standard-of-care for telemedicine visits as they are for face-to-face, in person visits.

T2DM is particularly well-suited to telemedicine since it can provide an effective way to monitor and provide much-needed educational and motivational support to patients with this diagnosis (21, 22, 23, 24). In light of the fact that T2DM affects minority populations in large numbers, telemedicine studies have focused on under-served populations with successful results (21, 25).

Additionally, although some studies of older adults from minority and medically underserved communities have noted a proportion of patients with lower levels of computer familiarity, this digital divide can be successfully addressed with patient education and development of smaller, more portable, and easier to use devices and technologies, which are rapidly evolving (21).

Previous studies have used many such tools and devices to great effect. For example, bluetooth-enabled blood glucose meter linked to a mobile app was used successfully as part of the diabetes intervention, which also included a standard algorithm for self-titration with an electronic diary to record insulin doses integrated into the software; participants were provided with immediate feedback of their blood glucose data, and nurses provided review and follow-up via video and/or phone (22). In such studies, the engagement of nurses, who are consistently accessible to address various routine questions about titration protocols or telemedicine procedures, is seen as highly valuable (22, 23). Overall, the support team approach, which includes not only nurses but also dietitians and potentially certified diabetes educators (CDEs) in addition to physicians, was effectively utilized in rural, underserved, and ethnically diverse settings (25), and no differences were noted regarding intervention provided by nurses compared to physicians.

Studies also report participants’ enthusiastic engagement with the telemedicine model (22) and quick adoption of it, even in cases where some additional training needed to be provided. With 64% to 68% of adults in America owning a smartphone in 2015 vs 35% in 2011, the use of smartphones is steadily increasing, and this increase is evident across ages and ethnic groups. As 45% of American adults who own a smartphone are reportedly using it to manage various aspects of their lives including their health, transition to telemedicine should be seamless.

In addition, some public and private payors are now accepting telemedicine for diabetes management, and with the demonstrated evidence that proactive management is helping patients avoid damaging and costly complications (such as blindness, amputations, etc) this trend is likely to continue.

Taking all these factors into consideration, certain participating sites will be designated as a virtual study model. As part of this model, certain study visits will be completed using telemedicine technology; additional aspects of this model are outlined throughout the protocol/virtual site model Project Plan where they differ operationally from traditional study sites.

The primary objective of the current study is to demonstrate the superiority of Soliqua 100/33 versus Lantus in the hemoglobin A1c (HbA1c) change from baseline to Week 26 in both the overall population and within each ethnic/racial subgroup evaluated (ie, Hispanics of any race, non-Hispanic black/African Americans, and non-Hispanic Asians). Patients enrolled in the trial will be insufficiently controlled on basal insulin and 1 or 2 oral antidiabetic (OAD) agents. Additionally, multiple secondary and “other” endpoints will be evaluated, focusing not only on glucose-lowering effects and HbA1c but also on hypoglycemia, body weight, need for rescue therapy, treatment dose, and patient-reported outcomes (PRO). These endpoints are considered appropriate to demonstrate the expected benefits of Soliqua 100/33 in the overall population and within each of the ethnic/racial groups evaluated. This objective is in line with the U.S. FDA’s strong interest in encouraging participation of a more diverse population in clinical trials (26).

Soliqua 100/33 is a combination of a long-acting human insulin analog with a GLP-1 receptor agonist initially approved in the U.S. in 2016, indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide. Other information concerning Soliqua 100/33 is available in the Soliqua 100/33 U.S. Package Insert (USPI) (27). The patient population selected for this study is consistent with the target population according to the approved label indication.

Lantus, an analog of human insulin, provides 24-hour blood glucose control after a single subcutaneous injection. Lantus has been marketed since June 2000 in Europe and since May 2001 in the U.S. and other parts of the world. Lantus is indicated for the treatment of adult and pediatric patients with Type 1 diabetes or adult patients with T2DM who require basal (long-acting) insulin for the control of hyperglycemia. Other information concerning Lantus is available in the Lantus USPI (28).

The current study (LixiLan-D, Diversity) will be an open-label, 1:1 randomized, active-controlled, 26-week duration, parallel-group, multicenter, U.S.-only, Phase 3b study to compare the efficacy and safety of Soliqua 100/33 to Lantus in the overall population and in ethnically/racially diverse groups. Patients with T2DM inadequately controlled on a background of basal insulin and 1 or 2 OAD agents will be enrolled. To ensure a balanced IMP allocation, randomization will be first stratified by self-reported ethnicity/race (ie, Hispanics of any race, non-Hispanic black/African Americans, and non-Hispanic Asians) and will be capped to allow randomization of approximately similar number of patients within each ethnic/racial subgroup. Randomization will be secondarily stratified by the screening HbA1c value (<8.5% versus ≥8.5%), the background

use of sodium glucose co-transporter 2 (SGLT-2) inhibitors (yes/no), and by the background use of sulfonylureas (yes/no).

The study will consist of 3 periods:

- An up to a 2-week screening period
- A 26-week open-label randomized treatment period: at the end of the screening period (Week 0, Visit 2) patients will be randomized to receive either Soliqua 100/33 or Lantus.
- A 3-day post-treatment safety follow-up period.

Patients who prematurely and permanently discontinue IMP administration during the randomized treatment period should continue all study visits and assessments per protocol (except for the follow-up visit). The maximum study duration per patient will be of approximately 29 weeks. This type of study design is considered adequate to address the objectives of the study.

Conclusion on the benefit risk assessment in this study

The IMPs administered in this study (Soliqua 100/33 and Lantus) have demonstrated glucose-lowering properties and are both approved for the treatment of adult patients with T2DM.

Given the safety profile observed during development, Soliqua 100/33 is considered well tolerated and with properties reflective of the individual components. No new risk has been identified for the population to be included in Study LPS14860. Treatment with both Soliqua 100/33 and Lantus is in line with current FDA-approved label indications. Therefore, the risk for patients participating in this study and using daily doses of Soliqua 100/33 up to 60 U of insulin glargine and 20 µg of lixisenatide is considered acceptable. All patients entering this study will receive treatment with Soliqua 100/33 or Lantus in combination with 1 or 2 OADs. As participants in the trial, all patients will benefit from close management of their T2DM. Rescue therapy is planned and described in the clinical study protocol for patients whose glycemia remains poorly controlled.

Given the expected improvement of metabolic control and the additional measures to improve diabetes management as part of the trial, these benefits are considered to outweigh any potential risk associated with Soliqua 100/33 and Lantus. Therefore, the benefit-risk ratio for patients participating in Study LPS14860 is considered favorable.

5 STUDY OBJECTIVES

5.1 PRIMARY

- To demonstrate the superiority of Soliqua 100/33 versus Lantus in the HbA1c change from baseline to Week 26 within the overall population.
- To demonstrate the benefit of Soliqua 100/33 versus Lantus in the HbA1c change from baseline to Week 26 within each ethnic/racial subgroup evaluated (ie, Hispanics of any race, non-Hispanic black/African Americans and non-Hispanic Asians).

5.2 SECONDARY

- To assess the effects of Soliqua 100/33 versus Lantus on the secondary efficacy parameters to Week 26 for the selected endpoint (see “Study Endpoints”) within each ethnic/racial subgroup evaluated.
- To assess the change from baseline to Week 26 in daily insulin glargine dose within each ethnic/racial subgroup.
- To evaluate the safety and tolerability (eg, gastrointestinal tolerability) of Soliqua 100/33 versus Lantus to Week 26 within each ethnic/racial subgroup.

5.3 OTHER

- To assess the effects of Soliqua 100/33 versus Lantus on other efficacy parameters to Week 26 for the selected endpoint (see “Study Endpoints”) within each ethnic/racial subgroup evaluated.
- To assess the effects of Soliqua 100/33 versus Lantus on efficacy and safety parameters to Week 26 in the overall population.
- To evaluate and compare the effect of Soliqua 100/33 versus Lantus on Patient Reported Outcome (PRO) measures to Week 26 within each ethnic/racial subgroup.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is an open-label, 1:1 randomized, active-controlled, 26-week duration, parallel-group, multicenter, US-only, Phase 3b study to compare the efficacy and safety of Soliqua 100/33 with Lantus overall and in ethnically/racially diverse groups with T2DM inadequately controlled on basal insulin and 1 or 2 OAD agents. The patients will be randomized according to their self-reported ethnicity/race (ie, Hispanics of any race, non-Hispanic black/African Americans and non-Hispanic Asians); randomization will be capped to include approximately similar numbers of patients (ie, 400) within each ethnic/racial subgroup, with approximately 200 patients per ethnic/racial group receiving Soliqua 100/33 and approximately 200 receiving Lantus. Additionally, to ensure a balanced IMP allocation, randomization will be stratified by their self-reported ethnic/racial group, screening HbA1c value (<8.5% versus ≥8.5%), the background use of SGLT-2 inhibitors (yes/no) and the background use of SUs (yes/no). Patients will participate in 1 of 2 ways, either at a traditional ‘brick & mortar’ investigational site, or fully remotely through a virtual (telemedicine) arrangement.

The study will consist of 3 periods:

- An up to 2-week screening period
- A 26-week open-label randomized treatment period: at the end of the screening period (Week 0, Visit 2) patients will be randomized to receive either Soliqua 100/33 or Lantus
- A 3-day post-treatment safety follow-up period (not required for patients who prematurely and permanently discontinued IMP administration but stayed in the study through Week 26; these patients should continue all study visits except for the follow-up visit).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The maximum study duration per patient will be of approximately 29 weeks (comprised of an up to 2-week screening period, a 26-week open-label randomized treatment period, and a 3-day post-treatment safety follow-up period).

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as being the “last patient last visit” planned within the protocol, including follow-up visit.

The Sponsor can terminate the trial prematurely at any time for any reason, including any unforeseen developments.

6.3 INTERIM ANALYSIS

No formal interim analysis is planned.

6.4 STUDY COMMITTEES

No study committees are planned.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. Patient with T2DM diagnosed for at least 1 year prior to the screening visit (signing of informed consent);
- I 02. Uncontrolled diabetes as demonstrated by a screening centrally measured HbA1c between 7.5% and 10% (inclusive);
- I 03. Patients who are Hispanics of any race, non-Hispanic black/African Americans or non-Hispanic Asians;
- Note:** Decision for ethnic/racial inclusion will be made based on the patient's self-identification. Mixed-race patients must select 1 of the above-mentioned categories. If such selection cannot be made, the candidate will be ineligible to participate in the study;
- I 04. Patients who have been treated with any basal insulin, ie, glargine 100 U/mL or 300 U/mL, detemir, degludec, intermediate-acting [human NPH]) for at least 6 months prior to Visit 1;
- I 05. The basal insulin regimen (ie, type of insulin and time/frequency of the injection) has been stable for at least 3 months prior to Visit 1;
- I 06. The basal insulin dose has been stable (defined as up to $\pm 20\%$ [1/5 of the dose] variability) for at least 2 months prior to Visit 1 within the following dose ranges:
- 15 to 50 units/day if HbA1c at Visit 1 is $\leq 8.5\%$ and
 - 15 to 40 units/day if HbA1c at Visit 1 is $> 8.5\%$
- I 07. Patients receiving 1 or 2 of the following OADs: metformin, pioglitazone/rosiglitazone, an SGLT-2 inhibitor or a SU, at stable doses for at least 12 weeks prior to Visit 1
- Metformin dose must have been ≥ 1500 mg/day or the Maximum Tolerated Dose (MTD), according to the Investigator's judgment;
 - Sulfonylurea dose must be \geq than the half maximum approved dose according to the local label. For patients with an HbA1c $< 8\%$, the SU dose must be reduced by 50% starting with the day of initiation of IMP administration; subsequently, the dose can be up-titrated according to the Investigator's judgment up to the dose previously taken by the patient. Additional increases in the SU dose (above baseline dose) should not be done unless the patient is rescued, according to the protocol rescue procedures.
- I 08. Patients willing and able to perform self-monitoring of plasma glucose (SMPG);
- I 09. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria which are sorted and numbered in the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

- E 01. Age <18 years of age at Visit 1;
- E 02. A body mass index (BMI) ≤ 20 or >40 kg/m² at Visit 1;
- E 03. Fasting plasma glucose (FPG) >200 mg/dL (by central lab measurement) at Visit 1 (1-time repeat measurement before Visit 2 is permitted);
- E 04. Type 1 diabetes mellitus or any diabetes other than T2DM;
- E 05. Any use of OAD drugs other than those described in the inclusion criteria (eg, but not limited to GLP-1 receptor agonists, DPP-4 inhibitors) within 12 weeks prior to Visit 1;
- E 06. Use of any other type of insulin except for basal insulin (eg, prandial or premixed insulin, insulin pump) within 6 months prior to Visit 1;
- Note:** History of short-term treatment (ie, ≤ 10 days) with other insulin types due to intercurrent illness is permitted at the discretion of the Investigator.
- E 07. Known history of discontinuation of treatment with a GLP-1 receptor agonist due to safety/tolerability reasons;
- E 08. Use of systemic glucocorticoids for a total duration of >7 days within 12 weeks prior to Visit 1;
- E 09. Initiation/change in type or dose of a weight loss drug within 12 weeks prior to Visit 1;
- E 10. Use of an investigational drug within 1 month or 5 times the duration of the pharmacodynamic effect, whichever is longer, prior to Visit 1;
- E 11. History of metabolic acidosis, including diabetic ketoacidosis within 12 months prior to Visit 1;
- E 12. History of stroke, myocardial infarction, unstable angina or heart failure requiring hospitalization within 6 months prior to Visit 1; planned hospitalization for any reason during the duration of the study;
- E 13. Known history of drug or alcohol abuse within 6 months prior to Visit 1;
- E 14. Clinically significant laboratory findings at Visit 1, including:
- Amylase and/or lipase >3 times the upper limit of the normal (ULN) laboratory range
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the ULN
 - Positive serum pregnancy test
- E 15. Conditions/situations such as:
- Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint (eg, sickle cell anemia, hemoglobinopathy or hemolytic anemia, severe anemia [screening Hgb <8.0 g/dL; transfusion indicated], receipt of blood or plasma products within 12 weeks of Visit 1),
 - Patients with conditions/concomitant diseases precluding their safe participation in this study (eg, active malignant tumor, clinically-significant psychiatric disorders, major systemic diseases, presence of clinically significant diabetic retinopathy or presence of macular edema likely to require treatment within the study period),

- Impossibility to meet specific protocol requirements (eg, scheduled visits, patients unable to fully understand patient's study documents and to complete them),
- Uncooperative patient or any condition that could make the patient potentially non-compliant to the study procedures (eg, patient unable or unwilling to do self-injections or blood glucose monitoring using the sponsor-provided blood glucose meter at home, etc),
- Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

- E 16. Any contraindication to Lantus use, according to local labeling;
- E 17. History of hypersensitivity to Lantus or to any of the excipients;
- E 18. Contraindications to the specific background OADs that each individual patient is taking (as applicable), according to the local label.

7.2.3 Exclusion criteria related to the current knowledge of Soliqua 100/33

- E 19. Contraindication to use of Soliqua 100/33 according to local labeling;
- E 20. History of hypersensitivity to Soliqua 100/33, or to any of the excipients;
- E 21. Pregnancy or lactation; women of childbearing potential (WOCBP) not protected by highly-effective contraceptive methods (as defined in the Informed Consent) and/or who are unwilling or unable to be tested for pregnancy; planning pregnancy during the duration of the study;
- E 22. Known history or presence of clinically-significant gastroparesis;
- E 23. History of pancreatitis (unless pancreatitis was related to gallstones and cholecystectomy has now been performed), pancreatitis during previous treatment with incretin therapies, chronic pancreatitis, pancreatectomy, stomach/gastric surgery;
- E 24. An estimated glomerular filtration rate (e-GFR) <30 mL/min/1.73 m² (more stringent renal function restrictions, depending on the patient's background OAD use are to be applied, according to the local label and the Investigator's judgment);

One-time re-test of screening laboratory values is allowed during the permitted screening period for this study (see [Section 10.1.4](#) for additional details). A patient must not be randomized more than once.

In case of screen failure due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the patient can be rescreened one time for this study. A new informed consent will be signed and a new patient number will be assigned by IRT for such subjects.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

The IMPs are Soliqua 100/33 (insulin glargine/lixisenatide) and Lantus (insulin glargine).

Table 2 provides a summary of each IMP.

Table 2 - Summary of investigational medicinal products

IMP	Soliqua 100/33	Lantus
Pharmaceutical Formulation	Soliqua 100/33 (insulin glargine/lixisenatide) is supplied for SC injection as a sterile aqueous solution in a 3:1 ratio SoloStar pen-injector. The prefilled disposable SoloStar pen-injector contains 3 ml of sterile solution of 100 U/mL insulin glargine and 33 µg/mL lixisenatide in a ratio of 3 U of insulin glargine to 1 µg lixisenatide and allows administration of daily combination doses between 15 U/5µg and 60 U/20µg.	Lantus (insulin glargine) is supplied for SC injection as a sterile aqueous solution in a prefilled disposable Lantus SoloStar pen-injector containing a 3 mL solution of insulin glargine 100 U/mL. The disposable SoloStar pen-injector allows for dose setting in the range of 1-80 U with a minimum dose increment of 1 U.
Dose, Timing and Route of Administration*	<p>Soliqua 100/33 should be self-administered by SC injection once daily in the morning in the hour (0 to 60 minutes) before breakfast.</p> <p>Starting dose for patients on a background basal insulin dose <30 U/day (at the time of randomization): 15 U of insulin glargine (corresponding to 5 µg lixisenatide).</p> <p>Starting dose for patients on a background basal insulin dose ≥30 U/day (at the time of randomization): 30 U of insulin glargine (corresponding to 10 µg lixisenatide).</p> <p>Note: The 20% dose reduction recommendation described for Lantus does not apply to Soliqua 100/33. Details on dose adjustments are presented in Section 8.1.1.</p>	<p>Lantus should be self-administered by SC injection once daily at any time of the day but at about the same time every day. The injection time will be determined at the discretion of the patient and Investigator at the time of randomization and it should remain about the same (±120 minutes) until the end of the randomized treatment period.</p> <p>The initial dose will be the same as the background basal insulin dose at which the patient is randomized unless transitioning from U300 insulin glargine, insulin administered twice daily or insulin detemir, when a 20% reduction in dose is required to initiate Lantus.</p> <p>Details on dose adjustments are presented in Section 8.1.1.</p>

IMP	Soliqua 100/33	Lantus
Storage conditions	<p>Prior to first use, Soliqua 100/33 pen should be stored in a refrigerator, 36°F to 46°F (2°C to 8°C). Do not freeze. Protect from light. Discard after the expiration date printed on the label. Each pen should not be used for more than 14 days after the first use.</p> <p>Soliqua 100/33 should not be stored in the freezer and should not be allowed to freeze. Discard Soliqua 100/33 if it has been frozen.</p> <p>After first use, store at room temperature below 77°F (25°C). Replace the pen cap after each use to protect from light.</p> <p>Discard pen 28 days after first use.</p> <p>Always remove the needle after each injection and store the Soliqua 100/33 pen without a needle attached. This prevents contamination and/or infection, or leakage of the pen, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.</p>	<p>Store new (unopened) pens in a refrigerator, between 36°F to 46°F (2°C to 8°C). Do not freeze. Store used (open) pens at room temperature, below 86 degrees F (30 degrees C). Do NOT store used (open) pens in the refrigerator. Store away from heat and light. If a Lantus SoloStar pen has been frozen or overheated, discard. Discard unrefrigerated or used pens after 28 days, even if they still contain medicine.</p> <p>Always remove the needle after each injection and store the Lantus pen without a needle attached. This prevents contamination and/or infection, or leakage of the Lantus pen, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.</p>

IMP: Investigational medicinal product; SC subcutaneous.

NOTE: Mixing of Soliqua 100/33 or Lantus with other insulins or dilution of solutions is not permitted.

* The first dose of IMP will be administered on the day of randomization (Day 1), either at the site (Soliqua 100/33 and Lantus on a morning dosing regimen) or outside the site location (Lantus administered on a regimen other than morning). If, due to logistical reasons, administration of IMP on the day of randomization is not possible, administration within 3 days following randomization is permitted.

8.1.1 Dose adjustments

The same dose adjustment algorithm is recommended for Soliqua 100/33 and Lantus.

The insulin doses will be up-titrated by 2 U or a maximum of 4 U/week (see algorithm in [Table 3](#)), until the patient reaches a target fasting SMPG of 80 to 100 mg/dL (4.4 to 5.6 mmol/L), inclusive, without clinically-significant hypoglycemia episodes.

Good clinical judgment should be exercised when titrating the basal insulin dose. Study patients should be trained and retrained on an ongoing basis to ensure proper understanding of titration procedures and a very close communication between the patient and the study site will be required to ensure adequate titration with minimization of associated risks.

Every effort should be made to reach the fasting SMPG target ranges by Week 12. Once the target SMPG has been achieved and until the end of the study, the basal insulin dose will be adjusted as necessary to maintain this fasting SMPG target.

Recommended dose changes are to be based on a median of fasting SMPG values from the last 3 days (including the day of titration) measured by the patient using glucometers and accessories supplied by the Sponsor.

For study sites using the virtual (telemedicine) study model, study staff will be available to patients to assist with any dose adjustments as needed and at any point during the study via telemedicine and/or phone and close communication with the study staff will be encouraged. Study patients will be continuously trained and re-trained to ensure proper understanding of titration procedures.

Table 3 details the dose adjustment algorithm for Soliqua 100/33 and Lantus.

Table 3 - Dose adjustment algorithm

Median of fasting SMPG values for last 3 days	Insulin glargine dose adjustments (U/day)
>140 (>7.8 mmol/L)	+4 ^a
>100 and ≤140 mg/dL (>5.6 and ≤7.8 mmol/L)	+2 ^a
Glycemic target: >80 and ≤100 mg/dL (>4.4 and ≤5.6 mmol/L), inclusive	No change
≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)	-2
<60 mg/dL (3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or 1 severe hypoglycemia.	-2 to -4 or at the discretion of the Investigator or medically qualified designee

a A titration dose increase of 2 or 4U for Soliqua 100/33 or Lantus may be split into 2 incremental dose steps, rather than implementing the entire dose increase at 1 time, if it is considered by the Investigator or medically-qualified designee to be in the best interest of the patient.
SMPG: self-monitoring of plasma glucose

8.1.1.1 Injection devices

Soliqua 100/33 and Lantus will be self-administered with a prefilled disposable SoloStar pen-injector.

The dose of Soliqua 100/33 is titrated according to the patient's need for insulin. Note that only the dose of insulin glargine appears in the pen dosing window. The dose (µg) of lixisenatide does not appear in the dose window even though lixisenatide is premixed in the cartridge.

Soliqua 100/33: prefilled disposable SoloStar pen-injector containing 3 mL of a sterile solution of 100 U/mL of insulin glargine and 33 µg/mL of lixisenatide in a ratio of 3:1 (3 units of insulin glargine per 1 µg lixisenatide).

The lixisenatide dose is thereafter increased or decreased along with insulin glargine dose changes.

Lantus: prefilled disposable SoloStar pen-injector containing Lantus are provided to patients randomized to the Lantus group at baseline (Week 0, Visit 2) and thereafter. Doses can be set from 1 to 80 units in steps of 1 unit.

Designated study sites using virtual study model will provide the IMP and all required study supplies via direct-to-patient shipments, as outlined in the virtual site model Project Plan. Shipments will be tracked and confirmed as delivered to patient by the study staff, with appropriate documentation in the patient study records. The IMP kit will be confirmed as received in good condition and within the acceptable temperature range (ie, fit for use). A virtual visit via

telemedicine will be completed to instruct patient on correct use and dosing of study medication, which will also be documented as part of the patient's study record.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

The protocol-mandated background OADs (Section 8.2.1) and rescue medication(s) used to treat hyperglycemia (Section 8.2.1) are considered non-investigational medicinal products (NIMP).

8.2.1 Background oral antidiabetic treatment

Patients in both treatment groups will continue with their permitted background OADs at stable doses and regimens until the end of the study unless there is a specific safety issue related to this treatment. Background OAD will be administered orally according to the locally approved label.

8.2.2 Rescue therapy

Rescue treatment is to be initiated, according to the Investigator's judgment in the event that at (or after) Week 12, HbA1c is >8%.

AND IF:

1. No explanation can be found for the insufficient glucose control (eg, infectious disease, lack of compliance with study treatment, non-compliance with diet and lifestyle requirements)
2. The appropriate actions to correct potential triggering factors fail
3. For patients randomized to Soliqua 100/33, an insulin glargine dose >60 units/day is necessary to decrease HbA1c below the threshold values (ie, further dose titration is not possible) and
4. The HbA1c value exceeding the threshold is confirmed by repeat test (performed at the central laboratory) approximately 4 weeks after the initial measurement (or at a time point considered appropriate by the Investigator).

Note: The 4-week HbA1c repeat may be waived if, according to the Investigator's judgment, the patient does not have any precipitating factors leading to an elevated HbA1c that must be addressed, and that it is in the best interest of the patient to initiate rescue immediately.

Rapid acting insulin (glulisine) is suggested as rescue therapy and it should be started as a once-daily regimen administered prior to the main meal of the day (excluding breakfast). If, according to the Investigator's judgement, rapid-acting insulin is not in the best interest of the patient, addition of an OAD (within the category of permitted background medications) or increases in the OAD doses already taken by the patient (according to the local label) may be considered as a secondary option for rescue therapy.

Note: GLP-1 receptor agonists are not permitted as rescue therapy.

After these assessments are completed and rescue therapy is initiated, the patient should remain in the study and continue to administer the study treatment (including background therapy). The planned visits and assessments should be performed until the last scheduled visit.

8.3 BLINDING PROCEDURES

This study is open-label.

8.3.1 Methods of blinding

This study has an open-label design with respect to treatment assignment (ie, Soliqua 100/33 and Lantus) and individual efficacy/safety data.

To compensate for the lack of blinding in the data review process, summary statistics (including for the primary efficacy parameter) will be tabulated by dummy treatment arm. The actual randomized treatment assignments will not be applied to aggregate summary statistics until the database has been locked for the primary analysis.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patients will be randomized at Visit 2 to one of the two following treatment arms:

- Soliqua 100/33 once daily, or
- Lantus once daily.

The randomization ratio is 1:1. The patients will be randomized according to their self-reported ethnicity/race (ie, Hispanics of any race, non-Hispanic black/African Americans, and non-Hispanic Asians); randomization will be capped to include an approximately similar numbers of patients (ie, 400) within each ethnic/racial subgroup, with approximately 200 patients per ethnic/racial group receiving Soliqua 100/33 and approximately 200 receiving Lantus. Additionally, to ensure a balanced IMP allocation, randomization will be stratified by the patients' self-reported ethnic/racial group, screening HbA1c value (<8.5% versus ≥8.5%), the background use of SGLT-2 inhibitors (yes/no), and the background use of SUs (yes/no).

The randomization and the treatment allocation are performed centrally by an interactive response technology (IRT). The randomized treatment kit number list is generated centrally by Sanofi and the Study Biostatistician provides the randomization scheme (including stratification) to the IRT. Then, the IRT generates the patient randomization list according to which it allocates treatment groups to the patients.

As part of the screening procedures the Investigator or designee has to contact the IRT vendor to receive the patient number. The patient identification (patient number) is composed of a 12-digit number containing the 3-digit country code (840 = USA), 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.).

A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The appropriate number of kits will be dispensed to provide patients with IMP coverage up to the next dispensing visit (please refer to [Table 1](#)). Storage conditions and use-by-end date are part of the label text.

Treatment labels will indicate the treatment number (used for treatment allocation and reported in the eCRF). The patient number, visit number, date of dispensation, and any other applicable information as required per site will be entered manually by the site staff on the treatment box label prior to dispensing.

Soliqua 100/33 SoloStar pens containing a 3 ml solution of insulin glargine 100 U/ml and lixisenatide 33 µg/mL are supplied as open-label treatment kits containing 3 prefilled Soliqua 100/33 SoloStar pens.

Lantus SoloStar pens containing a 3 ml solution of insulin glargine 100 U/mL are supplied as open-label treatment kits containing 3 prefilled Lantus SoloStar pens.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists, IMP managers) are responsible for storing IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The study sites that will employ the virtual (telemedicine) study model will have IMP shipped directly to study patients. These sites will receive IMP from sponsor and store it as required per protocol until ready to send to the patient per study schedule. IMP management software will be used for IMP accountability and management. Storage conditions are temperature-controlled, with continuous temperature monitoring and alarm system. All direct to participant IMP shipments require temperature controlled shipment conditions, be protected from light, and must not be frozen.

The expiry date is mentioned on the IMP labels and storage conditions are written on the IMP labels.

8.7 RESPONSIBILITIES

The Investigator or other personnel designated by the Investigator and allowed to store and dispense the IMP will be responsible for ensuring that IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's responsibilities and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly communicated to the Sponsor or designee. Some deficiencies may be recorded through a complaint procedure.

Certain defects in the quality of IMP may be subject to potential 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 IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

At each contact with the patient, either by phone/videoconference or during on-site visits, the Investigator or his/her medically-qualified designee must ask the patient about the administered doses of IMP (additional details are to be found in the study-specific operational documents).

Returned and dispensed IMP will be documented into tracking logs. Upon IMP return, a visual check has to be performed by site staff.

For NIMP OAD therapy, name, start and end date of treatment, total daily dose, etc, will be documented in the source documents and appropriate electronic case report form (eCRF pages). Compliance to NIMP OAD therapy will be checked by interviewing the patient at each visit and be documented in the source documents and in the eCRF.

8.7.2 Return and/or destruction of treatments

Patients within the traditional group (ie, 'brick & mortar' sites) have to return all used, in-use and unused IMP at either in-person visits or by mail (see more information below). Re-supply will be planned according to the study schedule (see [Table 1](#)), the in-use IMP and the upcoming planned doses.

Patients have to return all used, in-use, and unused IMP after completing their designated dose administrations for the open-label treatment period (or as part of their final assessment procedures in case of permanent premature discontinuation).

All used, partially used, or unused treatments will be retrieved by the Investigator. A detailed treatment log of the returned IMP will be established with the Investigator or other personnel designated by the Investigator, and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy any IMP unless the Sponsor provides written authorization. Authorization for destruction will be given by the Sponsor once reconciliation has been completed and all discrepancies have been resolved. Destruction can be performed by site if local regulation

permits and on capability of site; alternatively, study drug may be returned to the Sponsor or designee for destruction.

For NIMP, which is not provided by the Sponsor, returns and destructions are not required. Sites are required to appropriately maintain source documents and to record data in the eCRF as requested by Sponsor or designee.

For the designated sites using a virtual (telemedicine) study model, all used, in-use, and unused IMP will be returned to study site. Patients will collaboratively work with site staff to return IMP as required. Once returned, reconciliation will be completed and managed accordingly.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). Any treatment which are continued during the study or are initiated/changed during the study must be recorded in the source documents and the eCRF.

The following drugs are not permitted during the screening period or the treatment periods of the study:

- Any type of glucose-lowering agents other than the IMP (including insulins or OADs), authorized background anti-diabetic therapy and rescue therapy, if necessary;

Note:

- Short-term use (≤ 10 days) of short/rapid-acting insulin due to acute illness or surgery (eg, infectious disease) is allowed;
- If, according to the Investigator's judgment, rapid-acting insulin is not in the best interest of the patient, dose increases for concomitant OADs (except for up-titration of SUs) to manage uncontrolled hypoglycemia will be considered rescue therapy.
- Systemic (ie, oral or injectable) glucocorticoids for more than 7 days, whereas topical or inhaled applications are allowed with no time limit;

Any weight-loss medication, if applicable, should be maintained at a stable dose throughout the study duration.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary efficacy endpoint is the change from baseline to Week 26 in HbA1c (%).

Blood samples for HbA1c measurements will be collected at Screening and at study time points listed in [Table 1](#) and will be measured at a central laboratory.

If a patient needs to receive rescue antidiabetic medication or if a decision to permanently discontinue the IMP is made, an assessment of HbA1c should be performed before the introduction of rescue medication/permanent discontinuation. Following introduction of rescue medication, the patient should continue in the study and all study procedures according to the protocol should be performed.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

- Percentage (%) of patients achieving the HbA1c target of <7% at Week 26
- Change in 2-hour postprandial glucose (PPG) as measured utilizing a standardized meal test at Week 26 (for patients that performed the standardized meal test)
- Change in 2-hour glycemic excursions as measured utilizing a standardized meal test at Week 26 (for patients that performed the standardized meal test)
- Change from baseline to Week 26 in daily insulin glargine dose
- Change from baseline to Week 26 in body weight

9.2.2 Observation Period for Efficacy Variables

The on-treatment period for primary and other efficacy variables is defined as the time from the first injection of open-label IMP up to 14 days for HbA1c; 0 days for standardized meal test parameters and SMPG and insulin glargine dose; 1 day for FPG; and 3 days for body weight after the last injection of IMP or up to the introduction of rescue therapy, whichever is the earliest.

9.2.3 Safety endpoints

- Hypoglycemia
 - Documented hypoglycemia (plasma glucose values ≤ 70 mg/dL [3.9 mmol/L])
 - Symptomatic hypoglycemia
 - Documented hypoglycemia (plasma glucose values < 54 mg/dL [3.0 mmol/L])
 - Symptomatic hypoglycemia
 - Severe hypoglycemia
- Adverse events (AEs), including gastrointestinal AEs

- Serious adverse events (SAEs)
- Adverse events of special interest (AESI): serious allergic/hypersensitivity reactions, pregnancy, ALT >3 times the upper limit of normal, pregnancy, and symptomatic overdose of IMP/NIMP
- Vital sign parameters (change from baseline)

9.2.4 Observation Period for Safety Variables

The observation period for safety data will be divided into 3 segments:

- The pre-treatment period is defined as the time between the date of signing of the informed consent and the first injection of IMP,
- The on-treatment period is defined as the time from the first injection of IMP up to and including 3 days after the last injection of IMP (treatment-emergent AE [TEAE] period),
- The post-treatment period is defined as the time starting 4 days after last injection of IMP (after the TEAE period).

9.2.4.1 Hypoglycemia

See [Section 10.7.2](#).

9.2.4.2 Adverse events

Refer to [Section 10.4](#) for details.

9.2.4.3 Vital signs

Vital signs (systolic and diastolic blood pressure, heart rate) will be measured in sitting position (patient must be sitting for approximately 5 minutes prior to the measurements).

9.3 OTHER ENDPOINTS

9.3.1 Other efficacy endpoints

- HbA1c change from baseline to Week 12
- Fasting plasma glucose change from baseline to Week 26
- Percentage of patients requiring rescue therapy by Week 26
- Percentage of patients reaching the HbA1c target of <7% at Week 26 with no body weight gain
- Percentage of patients reaching the HbA1c target of <7% at Week 26 with no documented symptomatic hypoglycemia (SMPG ≤ 70 mg/dL [3.9 mmol/L])
- Percentage of patients reaching the HbA1c target of <7% at Week 26 with no documented symptomatic hypoglycemia (SMPG <54 mg/dL [3.0 mmol/L])
- Percentage of patients reaching the HbA1c target of <7% at Week 26 with no body weight gain and no documented symptomatic hypoglycemia (SMPG ≤ 70 mg/dL [3.9 mmol/L])

- Percentage of patients reaching the HbA1c target of <7% at Week 26 with no body weight gain and no documented symptomatic hypoglycemia (SMPG <54 mg/dL [3.0 mmol/L])
- PRO measures:
 - Treatment Related Impact Measure – Diabetes (TRIM-D)
 - Patient and Physician Global Treatment Effectiveness Evaluation Scales

9.3.1.1 Fasting plasma glucose

Fasting plasma glucose samples will be taken according to the schedule listed in [Table 1](#) and measured by a central laboratory.

9.3.1.2 Percent of patients requiring rescue therapy

The use of rescue medications for hyperglycemia will be assessed up to Week 26 of treatment.

9.3.1.3 Soliqua 100/33 and Lantus doses

The patients are to record their IMP dose daily or any missed IMP injections in the patient diary.

9.3.2 Patient reported outcome endpoints

- TRIM-D;
- Patient and Physician Global Treatment Effectiveness Evaluation Scales.

9.3.2.1 Treatment Related Impact Measure – Diabetes

The general treatment-related impact on patients' health related quality of life, treatment satisfaction and treatment behavior will be assessed using the TRIM-D questionnaire according to the schedule listed in [Table 1](#).

The TRIM-D questionnaire (see [Appendix B](#) for an example) is a 28-item measure with 5 domains assessing Treatment Burden, Daily Life, Diabetes Management, Compliance and Psychological Health. This PRO measure can be scored independently for each domain or as a total score.

The 5-point Likert like response options, for all items, range from (1) Not at all satisfied/convenient, Never to Extremely/Almost always, Always or Extremely dissatisfied/inconvenient to (5) Extremely satisfied/convenient, depending upon the item stem and are scored on a scale of 0 to 100 so that a higher score indicates a better health state (less negative impact).

The TRIM-D variables include TRIM-D scores (total and domain scores) and the change in TRIM-D scores from baseline to endpoint.

A domain score is calculated if a respondent answers at least half of the items in a multi-item domain (or half plus 1 in the case of domains with an odd number of items).

9.3.2.2 Patient and Physician Global Treatment Effectiveness Evaluation Scales

Patient- and physician-rated global treatment effectiveness evaluation scales are instruments that will be measuring whether patient's overall response to treatment is excellent, good, moderate, poor, or whether the patient's condition is worsening. The variables related to these patient-rated and physician-rated global treatment effectiveness scales include the response to each question, given according to the schedule listed in [Table 1](#).

Example patient- and physician-rated global treatment effectiveness evaluation scales are provided in [Appendix C](#).

9.3.3 HbA1c measurement

For the eligibility and efficacy assessments of the study, HbA1c will be measured by a central laboratory to allow estimation of the change from baseline to Week 12 in HbA1c and other HbA1c endpoints (eg, <7% at Week 26, <7% at Week 26 with no body weight gain, or <7% at Week 26 with no body weight gain and no documented symptomatic hypoglycemia, or <7% at Week 26 with no documented symptomatic hypoglycemia).

9.3.4 Standardized meal test

At least 75 randomized patients per treatment arm/race/ethnic group will undergo a standardized meal challenge to assess fasting and postprandial glucose (tested at a central laboratory), as well as the postprandial glycemic excursion, as part of the screening procedures and during Week 26.

The standardized liquid meal test contains approximately 530 calories per serving, 46 grams of total carbohydrate, 22 grams of protein, and 30 grams of fat. The composition and the quantity of the standardized meal must be identical throughout the study.

If a patient participating in the standardized meal test needs to receive a rescue antidiabetic medication, the standardized meal test should be performed before the introduction of the rescue medication and at the end of the study (Week 26).

In case of permanent discontinuation of treatment with IMP, the standardized meal test should be performed only if the patient receives treatment on the day of the visit. The meal test should also be performed at the end of study as planned.

If the patient drops out of the study, at the time of IMP discontinuation, regardless of whether the patient received IMP or not on the day of the meal test, the meal test should be performed.

On the day of the standardized meal test, the patients must not eat any food or drink, except water, for at least 8 hours before the scheduled meal test (to be completed in the morning, if possible). Patients in the Soliqua or Lantus AM dosing groups will inject their treatment 30-60 minutes prior to the meal. Patients in the Lantus PM dosing group will inject their Lantus at their usual injection time.

The standardized meal for all patients should be consumed within a 15-minute period.

Blood for plasma glucose is drawn 5 times:

- 30 minutes prior to the start of the meal (during Screening and at end-of-treatment for patients randomized to the Lantus PM dosing group) or before IMP administration (at Week 26 for the Soliqua 100/33 arm and for the Lantus AM dosing group);
- Just before the start of the standardized meal (Minute 0), at least 30 minutes after the Soliqua or Lantus AM dosing injection;
- 30 minutes after the start of the standardized meal;
- 60 minutes after the start of the standardized meal;
- 120 minutes after the start of the standardized meal.

NOTE: On the day of the Week 26 (end-of-treatment) standardized meal test, morning IMP administration (ie, for the Soliqua 100/33 arm and for the Lantus patients administering IMP in the morning before breakfast) must be done within the interval between the initial (-30 minutes) plasma glucose collection and the Minute 0 plasma glucose collection. The exact times of the IMP injection and the standardized meal intake and the blood draws are to be documented.

Patients who are participating as part of the designated virtual study model will complete this meal test at a local laboratory testing facility.

9.3.5 Self-monitored plasma glucose

The SMPG will be used to titrate and adjust IMP doses, monitor glycemic control, and also as part of hypoglycemia management ([Section 8.2.2](#)). The fasting SMPG should be measured by the patient before breakfast and before the administration of IMP at least once a day starting from Week 0 until target FPG has been met; subsequently, the frequency of SMPG measurements can be reduced, according to the Investigator's judgement, however it should be done at least 3 times per week. Patients on PM Lantus dose should perform SMPG prior to administering their IMP. Additional SMPG measurements may be performed, as necessary during the study, including at any time when suspected symptoms of hypoglycemia are experienced by the patient.

SMPG during symptomatic hypoglycemia

Whenever patients experience hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate carbohydrate/glucose rescue prior to confirmation with the SMPG. Patients must contact the Investigator as soon as possible following significant events for review and for decision on any necessary actions to be taken.

9.3.6 Body weight

Body weight will be measured according to the schedule listed in [Table 1](#).

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. If possible, the same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer.

Body weight is read and recorded in source data and the eCRF. Self-reported weights are not acceptable; patients must not read the scales themselves.

Patients who are taking in the study as part of the designated virtual study model site will visit their local laboratory samples collection site to complete this measurement.

9.3.7 Dose of IMP

The study investigator/medically-qualified designee will obtain IMP dosing information during each on-site and remote (telephone, video) visit through a patient interview. At the minimum, details related to IMP dose and timing during the last 3 days prior to the visit, as well as information about any dose changes and IMP dosing interruptions will be collected from the patient's source documents and recorded as appropriate in the eCRF.

The Investigator will actively monitor the IMP dose on an ongoing basis in order to evaluate alignment with the protocol-recommended dosing algorithm.

9.4 APPROPRIATENESS OF MEASUREMENTS

The combination of basal insulin with a GLP-1 receptor agonist in a single daily injection is expected to lower HbA1c, with a complementary action on both fasting and postprandial glucose, with no or little weight gain or even weight loss, and a limited increased risk of hypoglycemia.

The primary efficacy analysis of this study comparing Soliqua 100/33 to Lantus will be based on the primary endpoint: change in HbA1c from baseline to Week 26 in the overall population and within the ethnic/racial sub-groups.

The concentration of HbA1c reflects the glycemic history of the previous 120 days and is thus an index of mean glycemia, documenting glycemic control over the past 2 to 3 months. Moreover, HbA1c has been shown to correlate with the development of long-term complications of diabetes, and reduction of HbA1c is known to reduce the risk of long-term microvascular complications. Therefore, HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control. In addition to the analysis of the change from baseline in HbA1c, the responder analysis allows the clinical relevance of the reduction observed in HbA1c to be demonstrated. The duration of study treatment is considered to be sufficient for achieving stable conditions with IMP and for enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia.

The problem of weight gain in T2DM is widely recognized. More than 80% of individuals with T2DM are overweight, many at the time of diagnosis. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycemic control. In this LixiLan-D (Diversity) study it is postulated that treatment intensification with the combination product will mitigate the burden of weight gain

that is typical when adding or uptitrating basal insulin. Taking into account the major impact of insulin-related body weight gain, it is appropriate to include body weight as an element of secondary and other endpoints.

Insulin glargine targets primarily, although not exclusively, fasting hyperglycemia, and lixisenatide effectively acts on postprandial glycemia mainly by slowing down gastric emptying. Therefore, assessment of both fasting and postprandial glucose (after a standardized meal) is relevant in this study. These two parameters are also considered by regulatory agencies to be supportive of efficacy of an antidiabetic agent.

Safety will be evaluated by standard clinical measurements and recording of any gastrointestinal events in particular. As both IMPs are approved products with well-established safety profiles, routine post-baseline laboratory testing are not planned in the study; however, “for-cause” assessments and evaluations will be performed as appropriate as part of AE/SAE management. Specific safety parameters of interest for a glucose-lowering injectable peptide such as symptomatic hypoglycemia, injection site reactions, and potential allergic reactions will also be assessed.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments listed in the “Study Flow Chart” in [Table 1](#) are not repeated in this section. The aim of this section is to provide details on how some of the procedures/assessments have to be performed.

This is an outpatient study and consists of up to 7 on-site visits (brick & mortar sites) or laboratory visits (for patients participating virtually through telemedicine) and 14 phone/video visits completed during the open-label randomized treatment period. Additional, optional phone/video visits to monitor insulin titration should be scheduled whenever considered necessary by the Investigator or designated site staff.

The patient has to be fasting for all sample collection procedures. As much as possible, these procedures should be completed in the morning, at approximately the same time. The patient should take OAD treatment and inject the Soliqua 100/33 or morning Lantus (if appropriate) after the fasting blood sample has been drawn. For patients administering Lantus in the afternoon or at bedtime, dose timing will be in the afternoon/evening, at times as agreed-upon between the patient and the Investigator at the time of randomization.

For the designated sites using the virtual study model, sample collection procedures will be completed at the local testing center.

The **fasting condition** is defined as an overnight fast of no less than 8 hours that consisted of no food or liquid intake, other than water.

Note: If the patient is not fasting at the time of blood collection visits (both for tradition and virtual sites), the blood sample will not be collected and a new appointment for laboratory samples collection should be made within the visit window, with instruction to be fasted.

10.1.1 Diet and Exercise

Lifestyle and diet counseling will be conducted during the study (in person and/or via telemedicine). This will be given by a medically qualified person (eg, registered dietician, diabetes educator, nurse, or physician) and should be consistent with the recommendations of the national or local guidelines for Type 2 diabetic patients (with regard to the distribution of calories among carbohydrates, proteins, and fats, exercise, etc.).

Compliance with the diet and lifestyle counseling will be discussed with the patient throughout the study and more specifically in case of insufficient glucose control (please refer to [Section 8.2.2](#)).

10.1.2 Glucometer, patient diaries and IMP titration training

All patients will be supplied with a glucometer, the corresponding supplies (lancets, test strips, etc.), a leaflet, and with electronic diaries at Visit 2/Week 0.

The glucometers should be calibrated according to instructions given in the package leaflet and the study personnel should also review the use of the glucometers with the patient regularly using the provided control solutions for data validity.

As part of the baseline procedures, patients are trained by the Investigator or qualified designee to appropriately utilize the glucometers and the associated supplies. Additionally, the patients will be trained on diary data entry (electronic diaries will be utilized in the study) and IMP titration requirements (see [Section 8.1.1](#)). Training is repeated as often as necessary during the study visits. It is the Investigator's responsibility to ensure appropriate training and re-training of the patients.

10.1.3 Hypoglycemia training

As part of the baseline procedures, patients are trained by the Investigator or qualified designee on the signs and symptoms of hypoglycemia, hypoglycemia unawareness and the appropriate corrective actions (including prompt timing), in order to ensure prevention and mitigation of serious/severe hypoglycemia occurrences in the study. Additionally, patients will be trained on the hypoglycemia diary 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. Training is repeated as often as necessary during the study visits. It is the Investigator's responsibility to ensure appropriate training and re-training of the patients. The Investigator will perform the medical validation of hypoglycemia reported by the study patients.

10.1.4 Screening period (Week -2 up to Week 0)

The screening period duration is up to 2 weeks, from the beginning of screening (Week -2) to the baseline visit (Visit 2, Week 0). During the screening period, participating patients will undergo the 2-hour standardized meal test, which will be completed as part of Visit 1.2 procedures ([Table 1](#)). This meal test can be performed at any time prior to Visit 2 procedures, once the patient's eligibility based on screening criteria has been confirmed. Once at least 75 randomized patients per treatment group/race/ethnicity have completed the screening meal test, this test may be stopped for that specific group, at the decision of the Sponsor.

Only patients who meet the inclusion criteria as noted in [Section 7.1](#) may be randomized. It will be the Investigator's responsibility to confirm that all eligibility criteria have been met prior to randomizing the patient.

During the screening period the patients should continue the anti-hyperglycemic treatment they were receiving prior to screening, ie, their background therapy (please see [Section 8](#) for details).

A one-time re-test of individual screening laboratory tests is permitted, if considered appropriate by the Investigator or if any of the laboratory test results are not available at the end of the screening period (eg, sample material damaged during transport). Exception to this rule is the HbA1c test, which cannot be re-tested during screening unless the result is missing or it is invalid. Exceptionally, if justified according to the Investigator and after discussion with the Sponsor or designee, the screening period can be extended by 1 additional week (7 days). This may occur in, but is not limited to, situations such as when source documentation (eg, from patient's primary physician) needs to be obtained to confirm the diagnosis of T2DM, when screening laboratory

results demand further clarification, in cases where there is a delay in IMP supply or when the patient requires additional training and time to demonstrate compliance. Randomization (Visit 2/Week 0) cannot be scheduled later than 3 weeks after initiation of screening procedures (ie, signature of the Informed Consent).

10.1.4.1 Visit 1 (screening visit, Week-2); Visit 2 (baseline visit, Week 0)

For the complete list and contents of procedures/assessments scheduled for the screening period, please refer to the “Study Flow Chart” in [Table 1](#).

The details of the procedures/assessments to be performed at visits during screening period and which are not described elsewhere are provided below:

Informed consent:

For both paper and electronic consent documentation processes, the patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration at the screening visit. Written information will be provided to the patient and must be signed by the patient and Investigator prior to starting any study procedures.

For those patients who are participating as part of the designated site using virtual study model, a secure link will be provided by the study staff to the electronic consent web portal via email, along with unique login credentials. Study investigator will complete the informed consent process with the patient by telephone/videoconference. Patients who agree to take part in the study will provide their handwritten signature using a computer mouse, touchscreen, or stylus on a computer tablet in the designated signature block, with study investigator countersigning.

Once consented, a study device (ie, study specific portable electronic device with preloaded study applications) will be sent out to study patients, along with any other supplies required for the screening visit, such as lab kits. Instructional information will be included in the delivery and delivery will be confirmed by study staff; fit for use of the study portable electronic device and study supplies will be confirmed as well via telephone/videoconference and further instructions will be provided, if needed. Additional study supplies will be sent to patients as needed throughout the study per study schedule, and all study supplies will be returned once study participation is completed.

Telemedicine visits and phone calls will be completed as needed throughout the screening period to collect the information noted below. Additional details are provided in the virtual site model Project Plan.

Demography, diabetes and medical/surgical history and medications:

Demography data that may include, but is not limited to age and/or birth date, gender, and ethnicity/race will be collected. Eligible patients must be one of the following: Hispanics of any race, non-Hispanic black/African American, or non-Hispanic Asian. The decision for ethnic/racial inclusion will be made based on the patient’s self-identification. Mixed-race patients must select one of the above-mentioned categories according to their self-identification. If such a selection cannot be made, the candidate will be ineligible to participate in the study.

Collection of diabetes history will include documentation of duration of diabetes and history of microvascular complications (retinopathy, neuropathy, and nephropathy). Medical/surgical history including patient's cardiovascular and allergy history and patient's family allergy history may be recorded. Medical records may be obtained and reviewed during the screening period.

A check of previous and/or current (concomitant) medications refers to documentation of all medications taken at any time during the 6 months prior to Visit 1, including the glucose-lowering agents (e.g., insulins, GLP-1 receptor agonists, OADs etc.) and all prescription/over-the-counter medications. In women of childbearing potential, the contraceptive methods have to be documented. Additional demographic and medical/surgical information may be collected, as appropriate.

Diet and lifestyle counseling:

Please see [Section 10.1.1](#).

IRT contact:

IRT will be contacted for notification of screening and patient number allocation ([Section 8.4](#)). The IRT contact should occur before any blood sample is drawn because the patient number is given by IRT and must be reported on the laboratory requisition forms.

Glucometer dispensation and training:

Please see [Section 9.3.5](#).

Central laboratory testing:

Blood and urine samples are collected for all central laboratory tests, as noted below, including those needed for confirming the patients eligibility for participation in the study.

Patients who are participating as part of the designated site using a virtual study model will complete blood/urine sample collection procedures at the local testing center. These locations are available across the country and provide standardized collection and processing of samples. Study staff will work closely with patients to arrange these visits. With the exception of screening and at Week 26, study patients who are not able to attend a local testing center will be able to complete these procedures via a home visit from a nurse or a phlebotomist. All necessary supplies to complete sample collections will be shipped to patient with instructions. All samples collected will be sent to a central laboratory facility for processing and analysis. For those patients participating in the standardized meal test during the screening period, refer to [Section 9.3.4](#).

Hematology tests will include erythrocytes, hemoglobin, hematocrit, leukocytes, and platelets. Serum chemistry tests will include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin (if >ULN, then the direct and indirect sub-fractions must be measured), creatinine, uric acid, sodium, and potassium. Urinalysis tests will include pH, glucose, ketones, leukocytes, blood/hemoglobin, and protein.

10.1.5 Open-label randomized treatment period (Week 0 to Week 26)

Patients meeting all eligibility criteria at the end of the screening period will be randomized into the open-label randomized treatment period. The duration of the open-label treatment period is 26 weeks \pm 3 days from baseline visit (Week 0, Visit 2) to the end-of-treatment visit (Week 26).

Each patient self-administers IMP (Soliqua 100/33 or Lantus) once daily from Week 0 (Visit 2) up to the end of the open-label treatment period (Week 26). The IMP dose will be adjusted according to fasting SMPG values ([Section 8.1.1](#)).

10.1.5.1 Baseline visit (Week 0; Visit 2)

For the complete list and contents of procedures/assessments scheduled for the baseline visit, please refer to the “Study Flow Chart” in [Table 1](#) and for detailed description of assessments in [Section 9](#).

The details of the procedures/assessments to be performed at this visit and which are not described elsewhere are provided below.

As part of this visit, all patients at traditional sites will complete a serum sample collection for calcitonin. A urine pregnancy sample collection procedure will be performed if the women are of childbearing potential. For patients that are women of childbearing potential and are participating as part of a designated site using the virtual study model, all pregnancy test will be serum and Visit 2 test may be done up to 1 week prior to the Visit 2 date (ie, it may be done at Visit 1.2, if the patient performs this visit; however, the results must be obtained prior to patient randomization). Calcitonin serum sample collection will be performed for all telemedicine patients before any study medication intake (at Visit 2 or Visit 1.2, if the patient performs this visit). Sample collection procedures will be completed at a local testing center. Additional baseline procedures will be completed via telemedicine.

Patients must fast for at least 8 hours prior to this visit (for IMP dosing purposes), and must not administer OAD(s) at home.

IRT contact:

After the screening assessments are completed and eligibility is confirmed, the Investigator or designated site staff contacts IRT for randomization. The treatment group (ie, Soliqua 100/33 or Lantus) is identified by IRT and patients will enter a 26-week open-label randomized treatment period.

An appointment for 1-week later is scheduled with the patient for the next visit.

10.1.5.2 Visits: Weeks 1-5 (Visits 3-7), Weeks 7-11 (Visits 9-13), Week 15 (Visit 15), Week 21 (Visit 17) and Week 24 (Visit 18)

The patient is contacted by the Investigator or qualified designee at a scheduled time. If the call or video visit has been completed by site staff other than the Investigator, the Investigator has to be consulted if an AE/SAE/other significant event (eg, severe/serious hypoglycemia) is suspected, and has to be informed in case an AE/SAE has occurred. In case of an AE, the patients may be asked to come to the investigational site, as appropriate. A phone/video visit can optionally be performed as a clinical visit in case of symptomatic hypoglycemia/AE or for other reasons.

Detailed instructions for the remote visits are provided in the appropriate study document.

An appointment should be scheduled for subsequent visits and a reminder for fasting requirements should be provided as necessary.

10.1.5.3 Visits: Week 6 (Visit 8), Week 12 (Visit 14) and Week 18 (Visit 16)

For the complete list and contents of procedures/assessments scheduled for the treatment period, please refer to the “Study Flow Chart” in [Table 1](#) and for detailed description of assessments to [Section 9](#). For virtual sites, these procedures will be conducted as per the virtual site model Project Plan.

The details of the procedures/assessments to be performed at visits and which are not described elsewhere are provided below.

Patients enrolled at designated sites using the virtual study model will complete their sample collection procedures at the local testing facility, where vital sign and body weight measurements will also be performed as required per study schedule. Additional study procedures for these visits will be completed via telemedicine and/or phone as appropriate.

Compliance check

Compliance check include compliance to IMP and OAD treatment and use of glucometer, review of daily fasting SMPG values, and patient diary.

For all visit procedures that include sample collection, patients are instructed to be fasting for 8 hours prior to the collection. The glucose meter measurement results, diary entries, and the used /in-use pens will be reviewed by the site staff, as required for these visits. When re-supply is planned/necessary, site staff will collect the unused pens from patients. If patient is not compliant to the study, the training has to be repeated by the site staff.

Upon completion of each visit, an appointment for the next visit will be made.

10.1.5.4 Final on-treatment assessment/end-of-treatment visit (Week 26 [Visit 19])

For the complete list and contents of procedures/assessments scheduled for the treatment period, please refer to the “Study Flow Chart” in [Table 1](#) and for detailed descriptions of assessments to [Section 9](#).

The same procedures/assessments including IRT contact as planned at Week 26 have to be performed in case of early permanent treatment discontinuation. The IRT has to be contacted in order to register the end of treatment.

Patients enrolled at sites using the virtual study model will complete the required sample collections and vital sign and/body weight measurement, as required per schedule, at the local testing center. Study staff and investigators will complete additional required study procedures with the patient via telemedicine and/or phone as appropriate.

An appointment for the post-treatment follow-up phone/video visit should be made.

10.1.6 Post-treatment follow-up visit (Week 26 +3 days [Visit 19 +3])

Following the last injection of Soliqua 100/33 or Lantus, either as scheduled or prematurely, a post-treatment follow-up phone/video visit is performed 3 (+3) days after the end-of-treatment visit for patients who complete the study or withdrew from the study at the time of IMP discontinuation. This visit can be a phone/video visit, a telemedicine visit for the designated sites using the virtual study model, or if needed a sample collection study visit in case of an ongoing or new adverse event during the post-treatment period, if necessary. The patient is called by the Investigator or medically qualified designee at a previously agreed-upon time point.

The post-treatment follow-up phone/video visit is not performed for patients who prematurely discontinue IMP treatment and stay in the study through Week 26.

Detailed instructions for the remote visits are provided in the virtual site model Project Plan.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in the patient’s file

Evaluations that are reported in the eCRF must be supported by appropriately identified source documentation, whether paper or electronic, for items below, but not limited to the following:

- Agreement and signature of informed consent mentioning the study identification;
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology;
- Contraception method for women of childbearing potential;
- Reason for lack of childbearing potential for concerned women (e.g. postmenopausal, history of hysterectomy);
- Previous and concomitant medication (including background OAD and rescue therapy);
- Study identification;

- Treatment kit number, dates of administration and doses of Soliqua 100/33 or Lantus Solostar pens;
- Compliance to background OAD therapy assessed by interview;
- Dates of visits and assessments including the examination report;
- Vital signs, height, body weight;
- Central lab reports received at site (dated and signed by the Principal Investigator or Sub-Investigator);
- IRT confirmation notifications by fax or e-mail (screening, screen failure, randomization, treatment reallocation, treatment/study discontinuation, treatment replacement if applicable, etc.);
- Adverse events and follow-up;
- In case of an SAE, the site should file in the source document, if obtained, at least copies of the hospitalization reports and any relevant examination reports (eg, imaging reports, specialists' reports, etc.) documenting the follow-up of the SAE or AESI;
- Date of premature study discontinuation (if any) and reason.

10.2.2 Source data verification requirements for patients not randomized

For patients not randomized, the source data that must be checked include the patient's identification details, the informed consent signed by the patient, the study identification, the dates of study visits and the main reasons preventing randomization.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study and complete all protocol-mandated procedures as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs or for other reasons. In case of treatment interruption due to an AE, reinitiating IMP treatment will be done under close and appropriate clinical/and or laboratory monitoring if the Investigator considers that the relationship of the event to the IMP is unlikely and if the study inclusion criteria are still met (refer to [Section 7](#)).

All durations of temporary treatment discontinuation should be recorded in the appropriate eCRF pages.

Temporary treatment discontinuation corresponds to more than 1 dose not administered to the patient.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is defined as any treatment discontinuation based on the Investigator or patient's final decision not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP, at any time and for any reason, or the Investigator may make the treatment discontinuation decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

Patients may withdraw from treatment with IMP at any time, for reasons including but not limited to the following:

- At patient's own request;
- If, in the Investigator's opinion, continuation with administration of IMP would be detrimental to the patient's well-being;
- At the specific request of the Sponsor.

A patient must withdraw from treatment with IMP in case of the following:

- Intercurrent condition that requires discontinuation of IMP: eg, diagnosis of acute pancreatitis confirmed by gastroenterologic evaluation and imaging and calcitonin value ≥ 50 pg/mL (14.75 pmol/L) or serious life-threatening hypersensitivity reaction;
- Pregnancy of patient.

Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent IMP discontinuation for the patient concerned.

10.3.4 Handling of patients after permanent treatment discontinuation

If possible, prior to permanent discontinuation of treatment regardless of the reason or as soon as possible after the decision for discontinuation has been made, the patients will undergo the procedure normally planned for the last dosing day with the IMP (Week 26/End-of-treatment visit).

Patients will be requested to continue the study procedures specified in this protocol up to the scheduled date of study completion (except for the Follow-up Visit), or up to recovery or stabilization of any AE, whichever comes last. More specifically, when treatment is prematurely discontinued before Week 26, all patients' data (efficacy and safety, including hypoglycemia) will be collected continuously up to the scheduled Week 26 visit unless the patient withdraws consent for any further participation in the study.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the eCRF and in the patient's source documents, as appropriate. The IRT should be notified when a patient prematurely discontinues treatment.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion at any time and irrespective of reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for study visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records when confirmed. At the minimum, the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to contact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The Statistical Analysis Plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening. Note: 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 which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event. Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive.
 - Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm;
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc);
 - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
 - Development of drug dependence or drug abuse;
 - ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN;
 - Suicide attempt or any event suggestive of suicidality;
 - Syncope, loss of consciousness (except if documented as a consequence of blood sampling);
 - Bullous cutaneous eruptions;
 - Cancers diagnosed during the study or aggravated during the study;
 - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

10.5 INTERIM ANALYSIS

No formal interim analysis for efficacy or safety is planned for this study. The study will not be terminated early for excellent efficacy.

10.5.1 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) 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. AESIs may be added or removed during a study by protocol amendment.

All AESI will be reported to the Sponsor in the same time frame as SAEs, ie, within 24 hours as detailed in [Section 10.4.1.2](#).

AESI are listed below:

- ALT >3 x ULN (see Appendix D)
- Serious allergic/hypersensitivity reactions (see [Section 10.7.1](#));
- Pregnancy occurring in a female patient administered IMP/NIMP;

Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.4.1.2](#)). In the event of pregnancy in a female patient, IMP should be discontinued. Follow-up of the pregnancy is mandatory until the outcome has been determined.

- Symptomatic overdose of IMP/NIMP. An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systemic pen counts) and defined as follows:
 - For Soliqua 100/33: any dose greater than 2-fold above the recommended/planned or prescribed dose administered per day within this clinical trial (ie, greater than 40 µg for lixisenatide and greater than 120 U for insulin glargine);
 - For Lantus: any dose administration which, in the Investigator's opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin;
 - For OADs: any dose greater than 2-fold above the recommended/planned or prescribed dose administered per day within this clinical trial.

The circumstances of the overdose (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

Note: Asymptomatic overdose with IMP does not need immediate notification; the definition is the same as described above. Asymptomatic overdose is to be reported in the standard AE page in the eCRF.

10.5.2 General guidelines for reporting adverse events

All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms (both the symptoms and the diagnosis should not be separately reported). The Investigator should specify the date of onset, severity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP/NIMP or by the study procedure(s).

The Investigator should take appropriate measures to follow all AEs that meet the serious criteria/AESI until clinical recovery is complete and laboratory results have returned to normal, until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that

additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. For non-serious AEs, the outcome at the time of last patient contact should be documented in the source documents and appropriate eCRF pages.

When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient or until the AE is resolved or stabilized.

Laboratory or vital signs abnormalities are to be recorded as AEs only if:

- Symptomatic and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion.

Instructions for AE reporting are summarized in [Table 4](#).

10.5.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of documentation for all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the eCRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.5.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.5.3](#), even if not fulfilling a seriousness criterion, using the screens in the eCRF.

Instructions for AE reporting are summarized in [Table 4](#).

Table 4 - Summary of adverse event reporting instructions

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety Complementary Form or equivalent	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest (non-SAE)	Expedited (within 24 hours)	Serious allergic/hypersensitivity reactions	Yes	Yes	Yes
		Pregnancy of female patient/subject	Yes	Yes	Yes
		Symptomatic overdose with IMP/NIMP*	Yes	No	Yes
		Increase in ALT	Yes	No	Yes
Adverse Event (non-SAE, non-AESI) leading to discontinuation	Routine	Others (eg, leading to IMP discontinuation)	Yes	No	Yes

*: Asymptomatic overdose is reported in the AE form and does not require expedited reporting.
AE adverse event; AESI adverse event of special interest; IMP investigational medicinal product, SAE serious adverse event.

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to IMPs to the regulatory authorities, according to local regulations.

Any AE not listed as an expected event in the Soliqua 100/33 or Lantus USPI will be considered as an unexpected event.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report (CSR).

10.7 SAFETY INSTRUCTIONS

10.7.1 Allergic or allergic-like reaction

If a patient experiences a serious allergic/hypersensitivity reaction, this has to be reported appropriately in the eCRF.

10.7.2 Hypoglycemia

Hypoglycemia will be evaluated in accordance with the 2017 joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes on reporting hypoglycemia in clinical trials (29).

The following categories of interest will be presented:

- **Documented hypoglycemia with plasma glucose cut-off of ≤ 70 mg/dL (3.9 mmol/L):** any hypoglycemia documented by a measured PG ≤ 70 mg/dL (3.9 mmol/L) regardless of symptoms.
- **Documented hypoglycemia with plasma glucose cut-off of < 54 mg/dL (3.0 mmol/L):** any hypoglycemia documented by a measure PG < 54 mg/dL (3.0 mmol/L) regardless of symptoms.
- **Severe hypoglycemia:** Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The definition of severe hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others.

Note that “requires assistance” means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident.

Clinical symptoms that are considered to result from a hypoglycemic 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.

Severe hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. All hypoglycemic events associated with seizure, unconsciousness or coma must be reported as SAEs. Only hypoglycemia events fulfilling the criteria of an SAE will also be documented on AE and SAE complementary forms in the eCRF.

Additional hypoglycemia categories that may be collected include (30):

- **Pseudohypoglycemia:** is an event during which the patient reports typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70 mg/dL (> 3.9 mmol/L).
- **Probable symptomatic hypoglycemia:** an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, (but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL [≤ 3.9 mmol/L]) ie, symptoms treated with oral carbohydrate **without** a test of plasma glucose.

All hypoglycemia episodes will be recorded by the patients in the study diary and that data will be incorporated in the eCRF or an associated, 21 CFR Part 11-compliant database, for access by the Investigator, local and central monitoring team, and or generation of the analysis data sets.

10.7.3 Local tolerability at injection site

If the Investigator or the patient recognizes any signs of local intolerance at the injection site, this should be recorded on the appropriate eCRF pages.

10.7.4 Monitoring of renal function in case of prolonged and severe nausea and vomiting

In case of prolonged or severe nausea and vomiting, if clinically indicated, serum creatinine measurement has to be centrally performed. If there is an acute increase of serum creatinine, and the patient is on metformin, this has to be discontinued until resolution of renal dysfunction.

10.8 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

All adverse events, including events noted above, will be continuously reviewed and recorded throughout the study by the study investigators. Patients who are participating as part of the designated site using the virtual study model will also be able to contact study investigators about adverse events as needed to either request an immediate telemedicine appointment or to discuss the event via a call with the study investigator and/or designated member of the study staff. Study investigator will coordinate participant's care and/or lab tests, procedures, and referrals as appropriate with the participant's local health care provider, and medical records from these appointments will be obtained. All reports will be documented as part of source documentation.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable change in HbA1c from baseline to Week 26, with the following assumptions, based on clinical trial data, along with additional modeling exercises (to evaluate the impact of the differences in study design between this study and the preapproval studies, eg, lack of placebo run-in):

- A common standard deviation of 0.95% and
- A true difference between Soliqua 100/33 and Lantus in mean change from baseline in HbA1c of 0.4%.

Calculations were made using nQuery Advisor[®] 7.0.

A total sample size of 1200 patients (400 per ethnic/racial group, 200 per treatment within each group) for inclusion in the intent-to-treat (ITT) population is planned. Two hundred patients per treatment/ethnic/racial subgroup would provide 96% power for superiority of Soliqua to Lantus in an individual ethnic/racial subgroup at the 1-sided 0.025/3 significance level. This would also provide 90% power for superiority in all 3 subgroups. In order to ensure an overall family-wise 2-sided error rate of 0.05, a Hommel procedure will be used.

Should barriers to recruitment exist within an ethnic group, [Table 5](#) gives examples of power achievable under the same assumptions of the treatment effect:

Table 5 - Alternate power calculations given recruitment shortcomings

Number of patients /ethnic group/treatment arm	Power for superiority at significant level of one-sided 0.025/3	power for superiority in all three subgroups if one of ethnic groups is under-recruited
180	94.5%	88%
150	89.4%	83%

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented in the CSR:

- Screened patients: patients who signed the informed consent;
- Randomized patients: patients with a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not;
- The safety population (ie, randomized and treated patients);
- The intent-to-treat (ITT) population (as defined in [Section 11.3.1](#) and analyzed as randomized);
- The randomization strata ie, patient's self-reported ethnic/racial group (ie, Hispanics of any race, non-Hispanic black/African Americans, and non-Hispanic Asians), HbA1c value

(<8.5% versus ≥8.5%), background use of SGLT-2 inhibitors (yes/no), and background use of SUs (yes/no) will be summarized by race/ethnic group. Any discrepancy between the strata assigned by IRT and the information reported on the eCRF will be listed for all randomized patients;

- Patients who completed the 26-week treatment period;
- Patients who discontinued IMP during the 26-week treatment period, and the reasons for treatment discontinuation;
- All patients who attended the Week 26 visit, regardless of whether they discontinued IMP during the 26-week treatment period;
- Patients who attended the Week 26 visit and had discontinued IMP during the 26-week treatment period.

For all categories of patients except screened patients, percentages will be calculated using the number of randomized patients as denominator for each treatment group.

A list of patients prematurely discontinued from treatment, along with reasons for discontinuation, will be provided.

Patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized will be identified and described in separate listings. For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy population

Efficacy analyses will be based on the ITT population, defined as all randomized patients. Patients will be analyzed for efficacy analyses according to the treatment group to which they are allocated by the IRT according to the randomization schedule at the randomization visit (as randomized), irrespective of the treatment actually received.

11.3.2 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who received at least 1 dose of open-label IMP, regardless of the amount of treatment administered. Patients will be analyzed for safety analyses according to the treatment actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.
- When a patient is exposed to different IMPs, the patient will be analyzed for safety in the treatment group (Soliqua 100/33 or Lantus) in which he/she was treated the longest.
- Patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken IMP.

11.4 STATISTICAL METHODS

Continuous data will be summarized by treatment group using the number of observations available, mean, standard deviation (SD), minimum, median, and maximum.

Categorical data will be summarized by treatment group using count and percentage.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by scheduled visits will be provided on observed cases (OC), ie, inclusion of only patients having non-missing assessments at a specific visit.

The baseline value is defined as the last available value before the first injection of open-label IMP or the last available value on or before the date of randomization if not treated with open-label IMP.

Analysis of demographics and baseline characteristics, prior and concomitant medications will be provided in detail in the SAP.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received in the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure will be assessed by the duration of treatment exposure during the study.

The duration of treatment exposure will be the total number of days of administration of open-label IMP, regardless of unplanned intermittent discontinuations.

The duration of IMP exposure will be calculated as:

(Date of the last open-label IMP injection – Date of the first open-label IMP injection) + 1.

The number (n) and percentage (%) of patients randomized and exposed to the open-label IMP will be presented by categories of cumulative exposure for each treatment group in the safety population. The time periods of interest will be defined in the SAP.

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) and cumulative exposure in patient-years will also be presented by treatment group in the safety population.

11.4.1.2 Compliance

Overall treatment compliance is defined as the actual number of days with IMP injection compared to the planned number of days with IMP injection during the open-label treatment period, up to treatment discontinuation. It is calculated according to the following formula:

$$\text{Compliance rate (\%)} = \left[\frac{\text{Total number of days with IMP injection}}{\text{Planned number of days with IMP injection}} \right] \times 100.$$

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance will be summarized by treatment group using mean, SD, median, and range for the safety population. In addition, the percentage of patients who have <60%, ≥60 to <80%, ≥80 to ≤100%, and >100% compliance will be summarized by treatment group.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of Primary Efficacy Endpoint

Analyses of the primary efficacy endpoint (change from baseline to Week 26 in HbA1c) will be performed using the ITT population, using HbA1c values obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or rescue medication use.

Primary analysis

The statistical test will be two-sided at a nominal 5% significance level (α level).

The change in HbA1c from baseline to Week 26 will be analyzed with missing values imputed by multiple imputation with the ‘jump to reference’ method. This approach assumes missing at random mechanism for missing data in the Lantus (control) group. However, it does not assume such a missing at random mechanism for missing data in the Soliqua 100/33 group. For a patient in the Soliqua 100/33 group, it assumes that the patient will lose the Soliqua 100/33 treatment benefit and uses the parameters of the Lantus (control) group to calculate the patient’s post-dropout mean response for the conditional mean in the imputation model.

- For patients in the Lantus group who have no HbA1c values at Week 26, the missing data will be considered as missing at random. Missing HbA1c values in this situation will be imputed by a regression imputation model where the model parameters are derived using the observed data from the Lantus group. The regression imputation model will include the patient’s baseline HbA1c values and randomization strata of ethnicity/race, SGLT use (Yes, No), and SU use (Yes, No) conditioned on the patient’s HbA1c values observed prior to dropout.
- For patients in the Soliqua 100/33 group who have no HbA1c values at Week 26, the missing HbA1c values will be imputed using a similar imputation model. However, prior

to dropout, the patient's mean response will be calculated using parameters that are derived based on the observed data from the Soliqua 100/33 group; post dropout, the patient's mean response will be calculated using parameters that are derived based on the observed data from the Lantus (control) group.

Each of the completed datasets will be analyzed by the analysis of covariance (ANCOVA) model with treatment groups, randomization strata of ethnicity/race, SGLT-use (Yes, No), and SU use (Yes, No), as fixed effects, and baseline HbA1c as the covariate. Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from baseline to Week 26 for each treatment group, as well as the between-group difference. If the upper bound of the 2-sided 95% CI for the adjusted mean difference (Soliqua 100/33 vs. Lantus) in HbA1c change from baseline to Week 26 is <0 , the superiority of Soliqua 100/33 will be declared. Details of the implementation of multiple imputation will be discussed in the SAP.

Summary statistics (for screening value, baseline value, observed values, and observed changes from baseline) at scheduled visits will be provided for each treatment group. The summary will include the number of observations, mean, SD, standard error (SE), minimum, median, and maximum.

As a secondary analysis to the primary efficacy endpoint, the treatment differences within each ethnic/racial subgroup will also be estimated from the adjusted means of the model.

Assessment of treatment effect by subgroup

Descriptive analyses will be performed on the primary endpoint to summarize the treatment effects across subgroups defined by the following baseline or screening factors:

- Race/ethnicity (Hispanics of any race, non-Hispanic black/African American, non-Hispanic Asian);
- Baseline HbA1c ($<8.5\%$, $\geq 8.5\%$);
- SGLT-2 (Yes, No) at screening;
- SU (Yes, No) at screening

Inferential comparisons of the treatment difference within each subgroup may be conducted and details will be discussed in the SAP.

11.4.2.2 Analyses of secondary efficacy endpoints

See [Section 9.2.1](#).

Analyses of the secondary efficacy endpoints will be performed using the ITT population for all patients and, separately, by race/ethnicity.

All categorical secondary efficacy endpoints defined for the 26-week randomized treatment period in [Section 9.2.1](#) will be analyzed using a logistic regression model adjusting for treatment group and appropriate baseline covariates. Details of the logistic model will be discussed in the SAP. The proportion in each treatment group will be provided, as well as the difference of

proportions between groups with associated 2-sided 95% CI. For the categorical secondary endpoints in which HbA1c is assessed at Week 26, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or introduction or rescue therapy. If no assessment is available at Week 26, patients will be treated as failures (non-responders).

Changes from baseline in 2-hour PPG, 2-hour glycemic excursions, daily dose of insulin glargine, and body weight will be tabulated by treatment group and visit, and details of inferential statistics to determine treatment differences will be discussed in detail in the SAP.

11.4.2.3 Multiplicity considerations

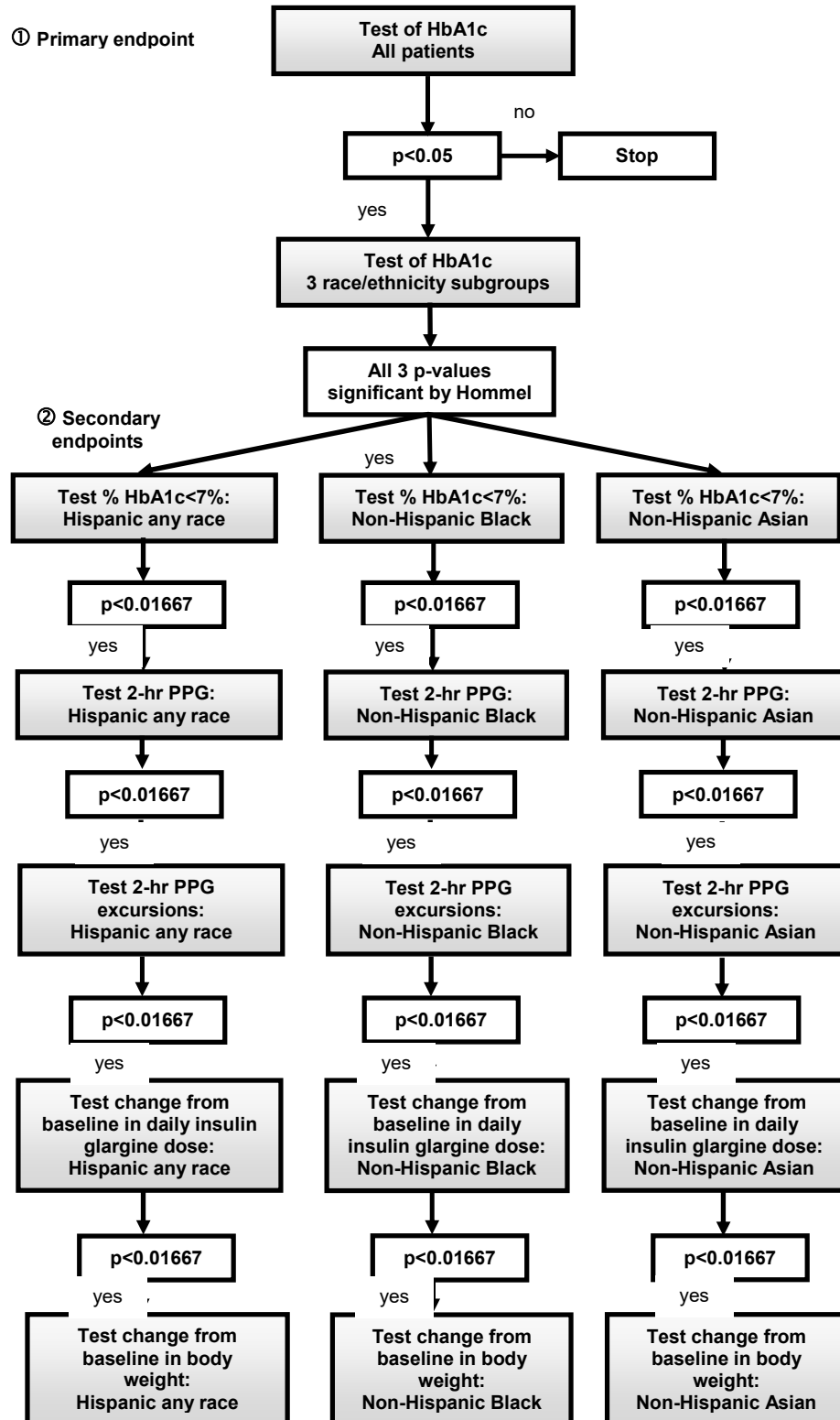
To control the familywise Type I error, two different strategies will be used for the family of hypotheses corresponding to the primary efficacy endpoints and the family of hypotheses corresponding to the secondary efficacy endpoints (please see [Section 11.4.2.2](#)).

For the primary efficacy endpoint (change from baseline to Week 26 in HbA1c) among all patients, no multiplicity adjustment is needed to control the Type I error since only 1 comparison of Soliqua 100/33 versus Lantus will be performed. If the hypothesis associated with the primary efficacy endpoint in all patients is rejected at the 5% level, the primary efficacy endpoint will be tested for each of the 3 race/ethnicity subgroups using the Hommel procedure. Specifically, if the largest p-value from the 3 ethnic/racial groups is less than or equal to 0.05, then statistical significance is achieved at all 3 ethnic/racial groups; if the largest p-value is greater than 0.05 but the second-largest p-value is less than or equal to 0.025 then statistical significance is achieved for the 2 ethnic/racial groups corresponding to the 2 smaller p-values; if the second-largest p-value is greater than 0.025 and the smallest p-value is less than or equal to 0.0167 OR the smallest p-value is less than or equal to 0.025 and the second-smallest p-value is between 0.025 (exclusive) and 0.0333 (inclusive), then statistical significance is only achieved for the ethnic/racial group corresponding to the smallest p-value.

If all 3 hypotheses associated with the ethnic/racial groups are rejected (statistically significant) for the primary efficacy endpoint, 2-sided 5% α level will be split equally among the 3 race/ethnicity subgroups (0.01667 for each) and the following secondary efficacy variables will be tested in the following prioritized order. *Testing will stop for a race/ethnicity subgroup when an endpoint is found not to be statistically significant at the 1.667% level:*

1. Percentage of patients achieving the HbA1c target of <7% at Week 26
2. Change in 2-hour PPG as measured utilizing a standardized meal test at Week 26
3. Change in 2-hour glycemic excursions as measured utilizing a standardized meal test at Week 26
4. Change in daily dose of insulin glargine from baseline to Week 26
5. Change from baseline in body weight to Week 26

Figure 1 - Multiple testing procedure



11.4.3 Analyses of other endpoints

Analyses of other endpoints defined in [Section 9.3](#) will be performed on the ITT population using all assessments obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy. Descriptive statistics will be summarized by treatment group. For selected other endpoints defined in [Section 9.3.1](#), descriptive statistics will also be summarized by treatment group for the whole study period.

11.4.4 Analyses of Patient Reported Outcome variables

The analyses of TRIM-D and global treatment effectiveness evaluation scales (patient- and physician-rated) will be performed on the ITT population.

Descriptive statistics (mean, median, standard deviation and range) for absolute values and for changes from baseline will be presented by treatment group per visit for each score.

The analyses of the patient-rated and physician-rated global treatment effectiveness evaluation scales will be performed on the ITT population. Patient- and physician-rated global treatment effectiveness evaluation will be presented in frequency and proportion by level of overall response to treatment (ie, complete control of diabetes, marked improvement of diabetes, discernible but limited improvement in diabetes, no appreciable change in diabetes, or worsening of diabetes) at the end of study for each treatment group.

Details on analyses for PRO variables will be discussed further in the SAP.

11.4.5 Analyses of safety data

See [Section 9.2.3](#).

The summary of safety results will be presented by treatment group for the 26-week randomized treatment period, unless specified otherwise.

All safety analyses will be performed on the safety population as defined in [Section 11.3.2](#) using the following common rules:

The baseline value is defined as the last available value prior to the first injection of open-label IMP.

The following definitions will be applied to laboratory parameters and vital signs.

- The potentially clinically significant abnormality (PCSA) values for clinical laboratory tests and vital signs are defined as abnormal values considered medically important by the Sponsor's Global Pharmacovigilance and Epidemiology department and in effect at the time of the final SAP approval. PCSA criteria for parameters not cited in the protocol as safety parameters will not be analyzed;
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.5.1 Analyses of adverse events

Pretreatment AEs are AEs that developed or worsened or became serious prior to the treatment period.

Treatment-emergent AEs (TEAEs) are AEs that developed or worsened (according to the Investigator's) or became serious during the on-treatment period.

Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

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

All adverse events

Adverse event incidence tables may present by SOC (sorted by internationally agreed order), high-level group term (HLGT), HLT and preferred term (PT) sorted in alphabetical order for each treatment group, 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 population within each treatment group.

Summaries of all TEAEs in each treatment group may include:

- The overview of AEs, summarizing number (n) and percentage (%) of patients with any
 - TEAE;
 - Serious TEAE;
 - TEAE leading to death;
 - TEAE leading to permanent treatment discontinuation;
- The number (n) and percentage (%) of patients with at least 1 TEAE by primary SOC, HLGT, HLT and PT;
- Summary of TEAEs by maximal severity (severe, moderate, mild), presented by primary SOC and PT;
- Summary of TEAEs possibly related to open-label IMP, presented by primary SOC and PT.

A detailed listing of TEAE summaries will be provided in the SAP.

Death and serious adverse events

Death and treatment-emergent SAEs will be summarized and presented as number (n) and percent (%) of patients in each treatment group.

Adverse events leading to permanent treatment discontinuation

TEAEs leading to permanent treatment discontinuation will be summarized and presented as number and percent of patients in each treatment group.

Local tolerability at injection site

AEs related to local intolerability at the injection site will be identified by searching the term “injection site” in the PTs coded from the Investigator reported terms. The number (%) of patients with related events will be summarized by treatment group.

Allergic reactions

The number (%) of patients with events as reported by Investigators and judged by the Investigator or Sanofi as possibly related to IMP will be summarized by treatment group. All allergic events reported by Investigators on the AE form for suspected allergic event and its associated complementary forms will be listed.

ALT increase

The number (%) of patients with events reported on the AE form for ALT increase and its associated complementary forms will be summarized by PT for each treatment group.

Gastrointestinal adverse events

The number (%) of patients with events reported on the AE form for gastrointestinal adverse events will be summarized by PT for each treatment group.

11.4.5.2 Analyses of hypoglycemia

See [Section 10.7.2](#).

The number (%) of patients experiencing a specific hypoglycemic event and the rates of the hypoglycemic event per patient year will be derived for each type of hypoglycemia (severe, documented [blood glucose ≤ 70 mg/dL and < 54 mg/dL]) and will be summarized by treatment group. The pattern of symptomatic hypoglycemia occurrence over time will also be assessed, if appropriate.

11.4.5.3 Analyses of vital sign variables

See [Section 9.2.4.3](#).

The number (n) and percentage (%) of patients with PCSA at any evaluation during the on-treatment period will be summarized for each vital sign parameter within each treatment group. The summaries will include patients in the safety population who have at least 1 parameter to be analyzed during the on-treatment period. When the PCSA definition involves the change

from the baseline value, patients need also to have a baseline value to be included in the summaries.

Descriptive statistics will be used to summarize the results for systolic and diastolic blood pressure and heart rate, and the changes from baseline by visit and for the last on-treatment value within each treatment group.

Tabular and graphical methods may be used to present the results for parameters of interest.

Listings will be provided with flags indicating the PCSA values.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written, either paper or electronic, informed consent form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form and any electronic platform used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure with any addenda or labeling documents [summary of product characteristics, package insert], Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol in an accurate manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

For the designated sites using virtual study model, remote study monitoring will be completed in addition to the on-site monitoring as described above. As part of remote monitoring, study monitors will be able to review electronic source documentation with view-only access, including medical records which will be available in each participant's study record. Trial-specific access to the electronic source records will be granted only the designated study monitors upon completion of training, which will be provided by the study site. Trial reports can be made available for review as well. Study monitors will issue queries and request resolutions, which will be completed by the study staff under supervision from the study investigators. All study-specific eCRF guidelines for resolutions will be followed.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, whether paper or electronic, except for the pre-identified source data directly recorded in the CRF, if applicable. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Sub-investigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations

Subject race or ethnicity (Hispanic of any race, non-Hispanic black/African Americans and non-Hispanic Asians) will be collected in this study because of the study objectives and also because these data are required by several regulatory authorities.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRBs/IECs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, good clinical practice, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Noncompliance of the Investigator or Sub-investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total planned number of randomized patients has been reached.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator agrees not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, with the understanding that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy.
6. Postmenopausal
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. However, in the absence of 12 months of amenorrhea, these patients should be considered to be of childbearing potential and should follow contraception guidelines accordingly.
 - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly^a</i>
<ul style="list-style-type: none">• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b<ul style="list-style-type: none">- oral- intravaginal- transdermal
<ul style="list-style-type: none">• Progestogen-only hormone contraception associated with inhibition of ovulation^b<ul style="list-style-type: none">- oral- injectable

Highly Effective Methods That Are User Independent
<ul style="list-style-type: none">• Implantable progestogen-only hormone contraception associated with inhibition of ovulation^b
<ul style="list-style-type: none">• Intrauterine device (IUD)
<ul style="list-style-type: none">• Intrauterine hormone-releasing system (IUS)
<ul style="list-style-type: none">• Bilateral tubal occlusion
<ul style="list-style-type: none">• Vasectomized partner <i>(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)</i>
<ul style="list-style-type: none">• Sexual abstinence <i>(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 study and the preferred and usual lifestyle of the subject.)</i>
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be used during the treatment period and for at least [XX, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which 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 procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination of a pregnancy will be reported as an AE or SAE.

- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in [Section 10.5.3](#). While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

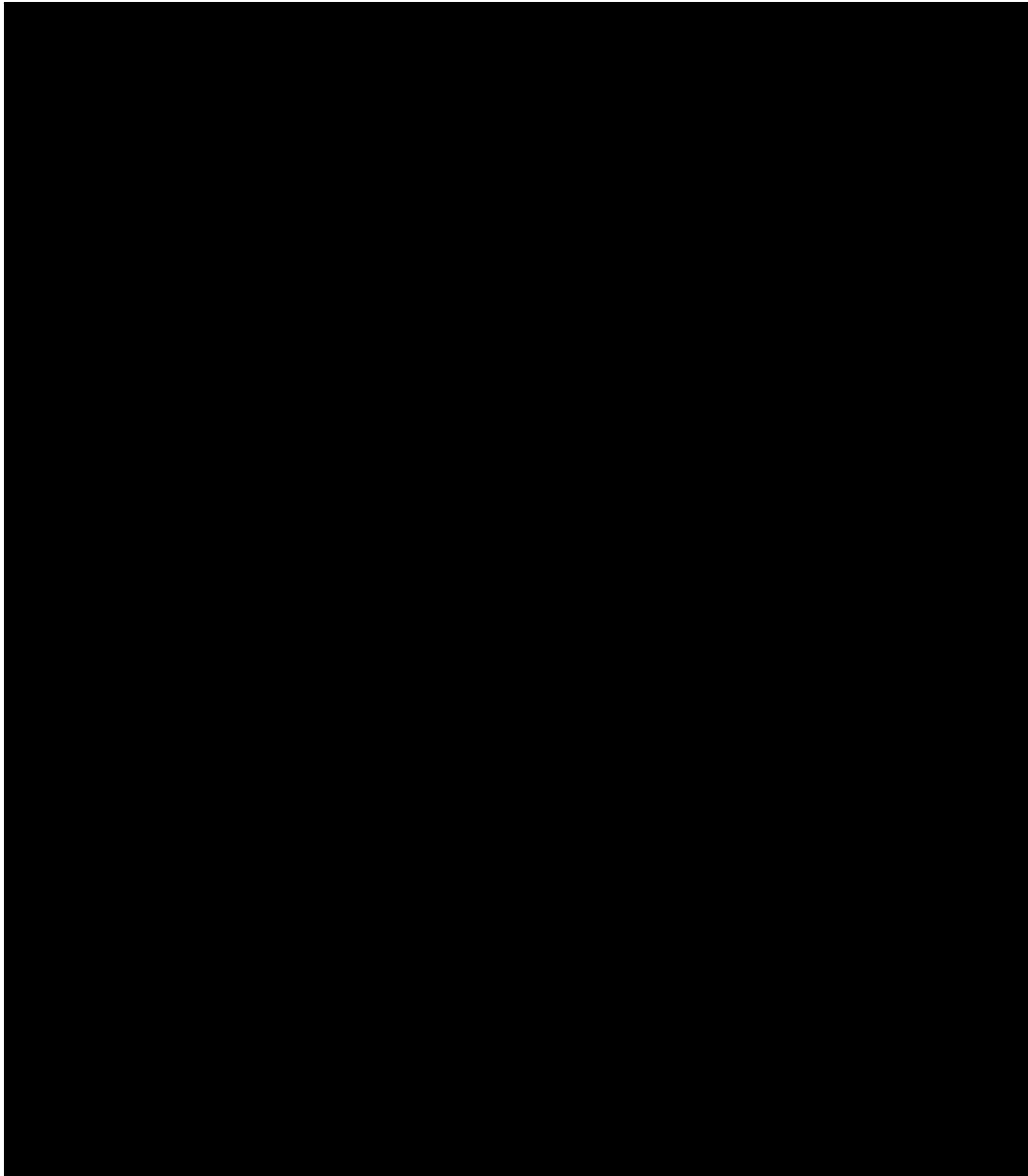
Appendix B

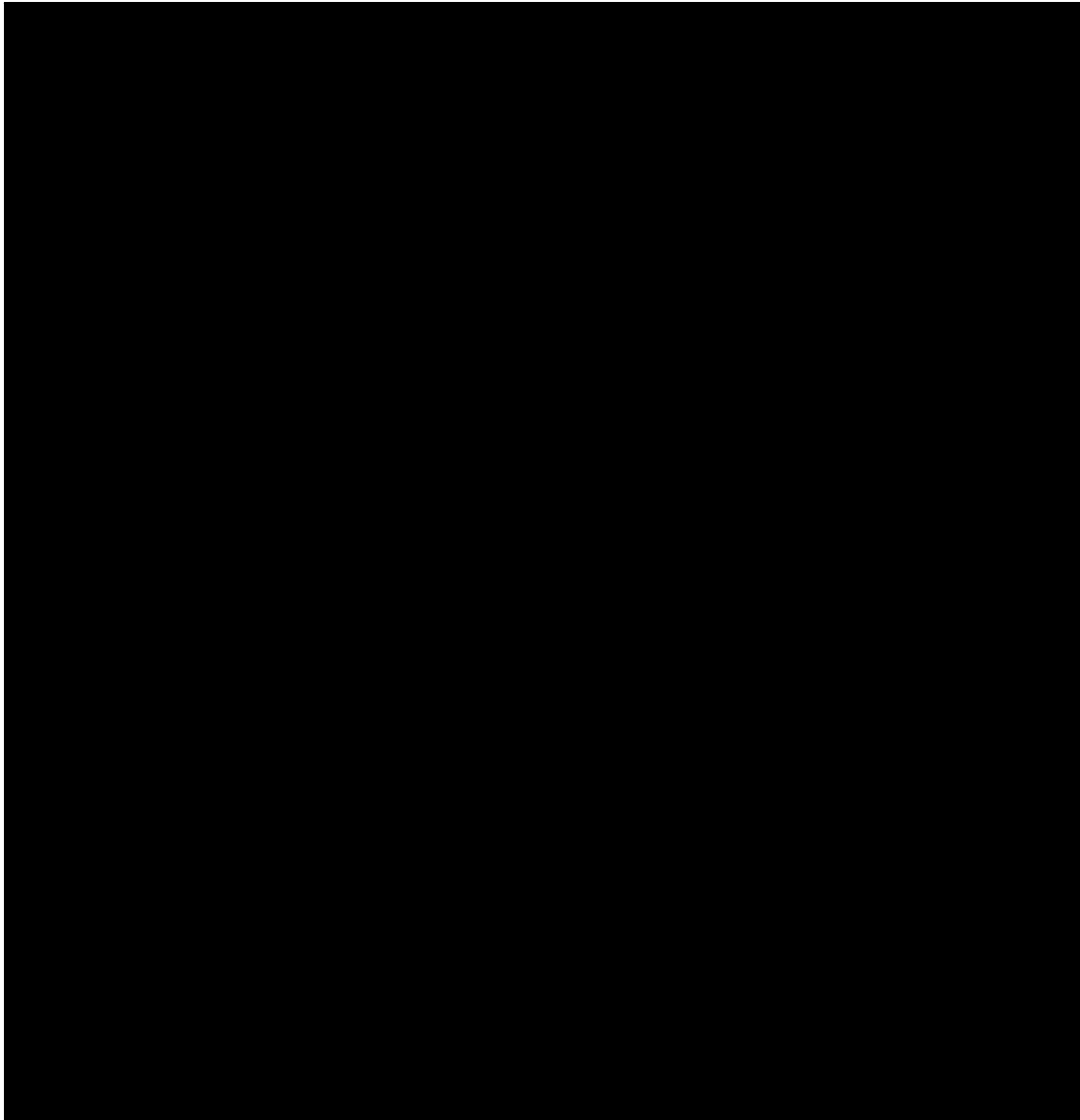
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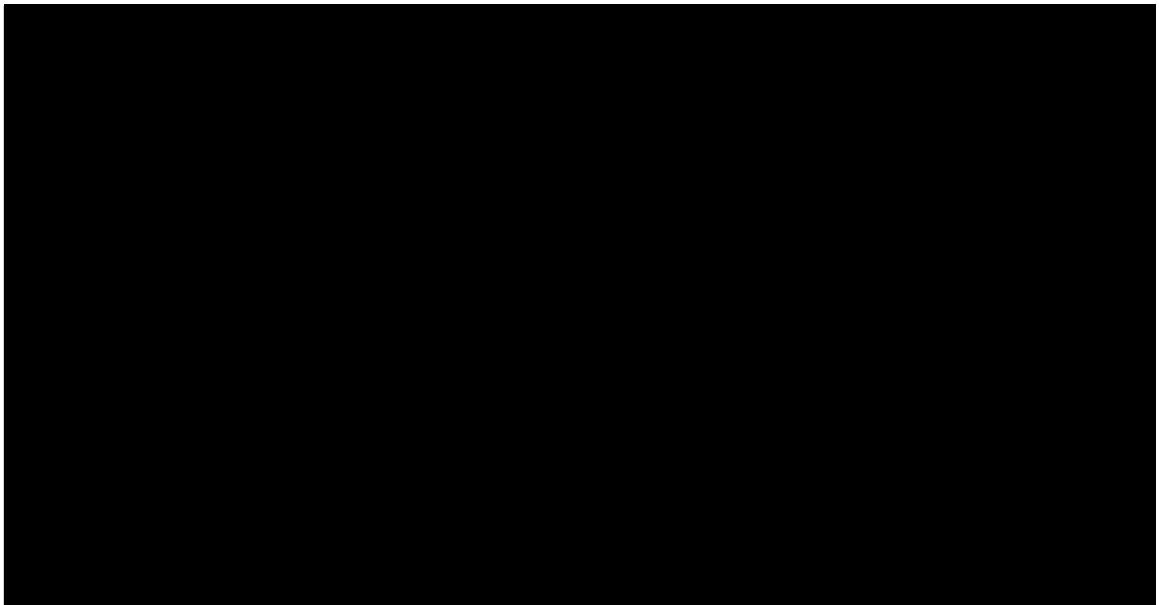
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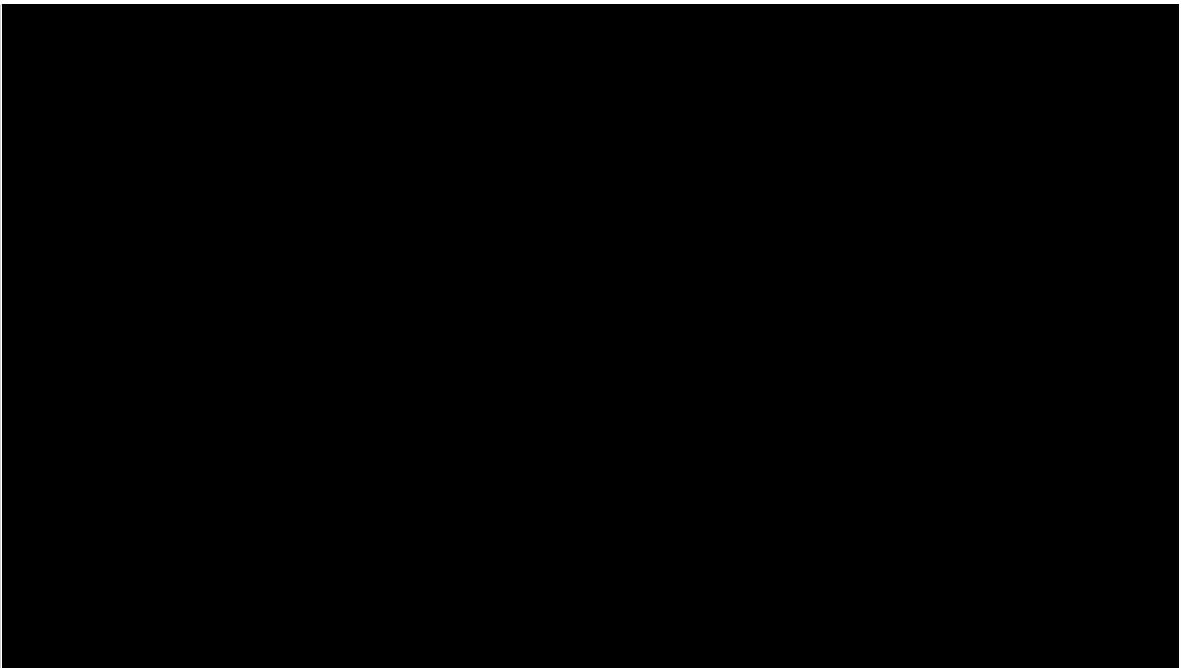
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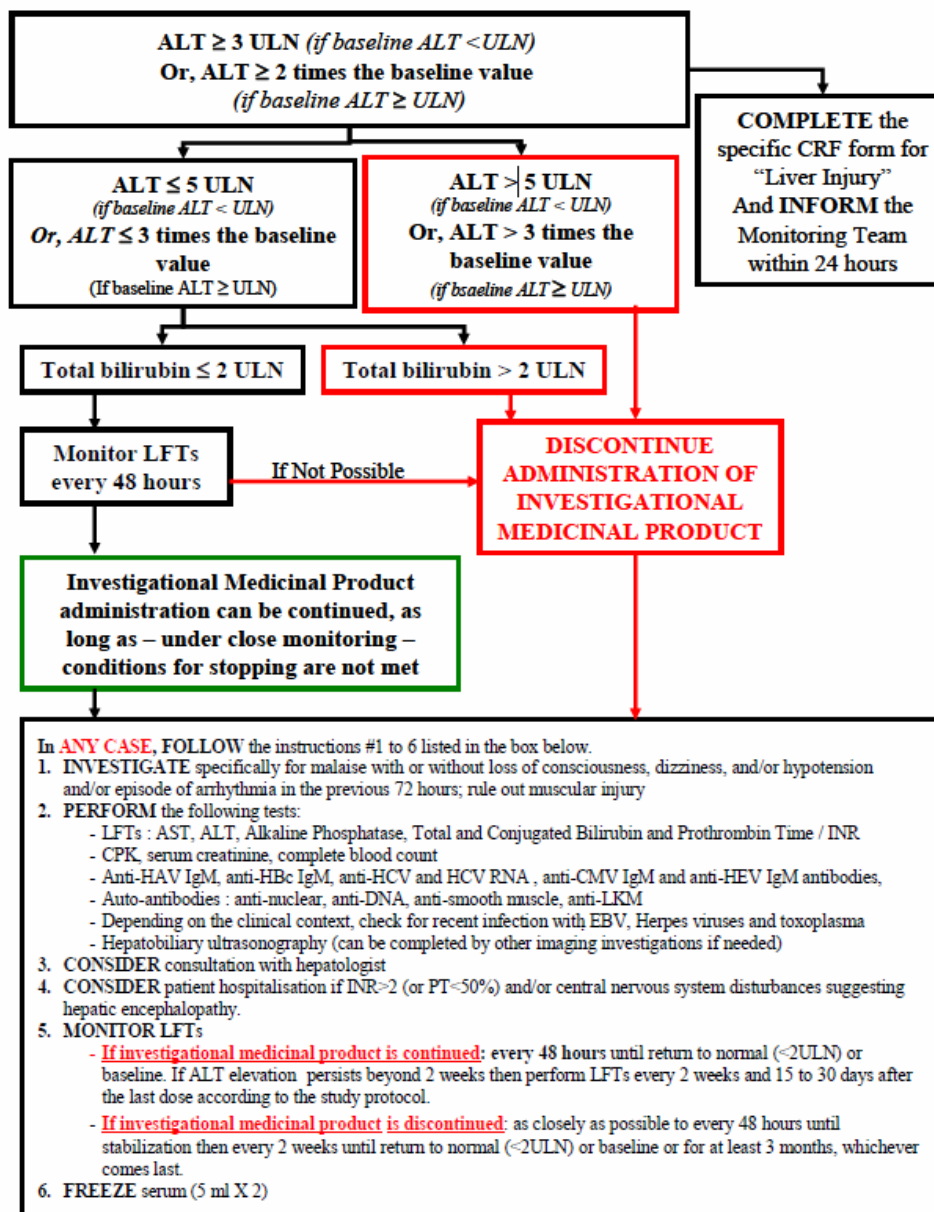
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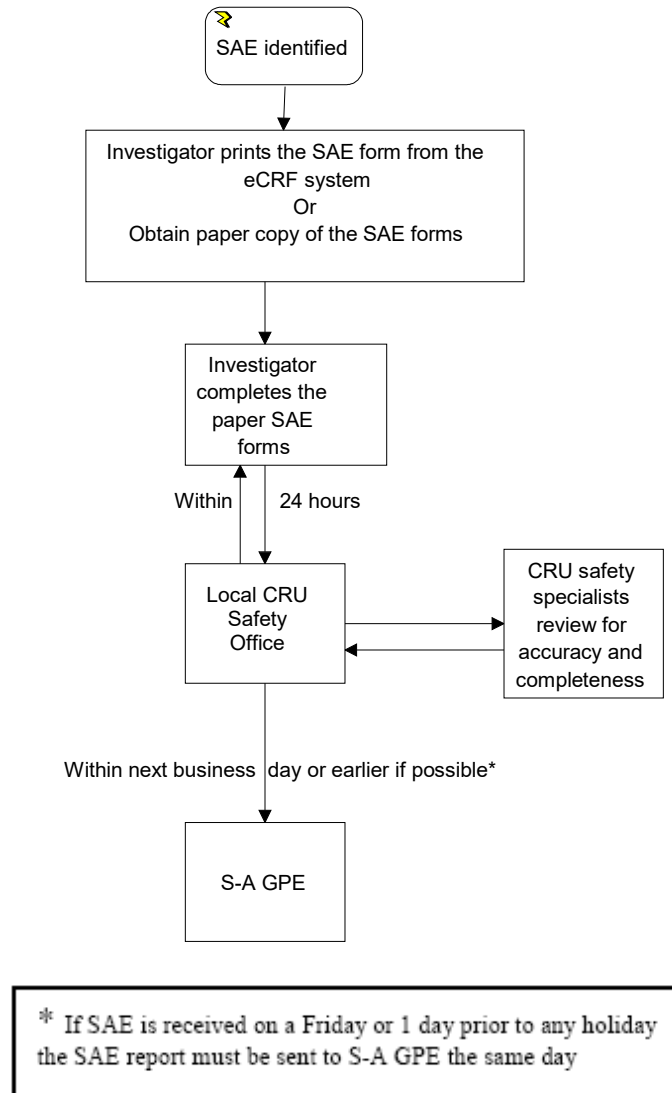


Appendix D General Guidance for the follow-up of laboratory abnormalities (ALT) by Sanofi

INCREASE IN ALT



Appendix E Back-up Plan for SAE and other Investigator Expedited Events reporting process when the eCRF system fails



LPS14860 16.1.1 Amended protocol 01

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
██████████	Clinical Approval	20-Dec-2017 14:44 GMT+0100
██████████	Regulatory Approval	20-Dec-2017 14:50 GMT+0100
██████████████████	Clinical Approval	20-Dec-2017 15:34 GMT+0100