NCT Number: NCT03434119

STATISTICAL ANALYSIS PLAN

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

Soliqua™100/33 -LPS14860

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AESI:	adverse event of special interest
BMI:	body mass index
DBP:	diastolic blood pressure
eCRF:	electronic case report form
HbA1c:	hemoglobin A1c
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IMP:	investigational medicinal product
ITT:	intent-to-treat
LLT:	lower level term
MedDRA:	medical dictionary for regulatory activities
OAD:	oral antidiabetic drug
OC:	observed case
PCSA:	potentially clinically significant abnormality
PPG:	postprandial glucose
PRO:	patient reported outcome
PT:	preferred term
SAE:	serious adverse event
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SMPG:	self-monitoring of plasma glucose
SOC:	system organ class
TEAE:	treatment emergent adverse event
WHO-DD:	world health organization-drug dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

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 (i.e., Hispanics of any race, non-Hispanic black/African Americans and non-Hispanic Asians). Additionally, to ensure a balanced IMP allocation, randomization will be stratified by their 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 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 though Week 26; these patients should continue all study visits except for the follow-up visit).

1.2 OBJECTIVES

1.2.1 Primary objectives

- 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 (i.e., Hispanics of any race, non-Hispanic black/African Americans and non-Hispanic Asians).

1.2.2 Secondary objectives

- To assess the effects of Soliqua 100/33 versus Lantus on the secondary efficacy parameters to Week 26 for the selected endpoint 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 (egg, gastrointestinal tolerability) of Soliqua 100/33 versus Lantus to Week 26 within each ethnic/racial subgroup.

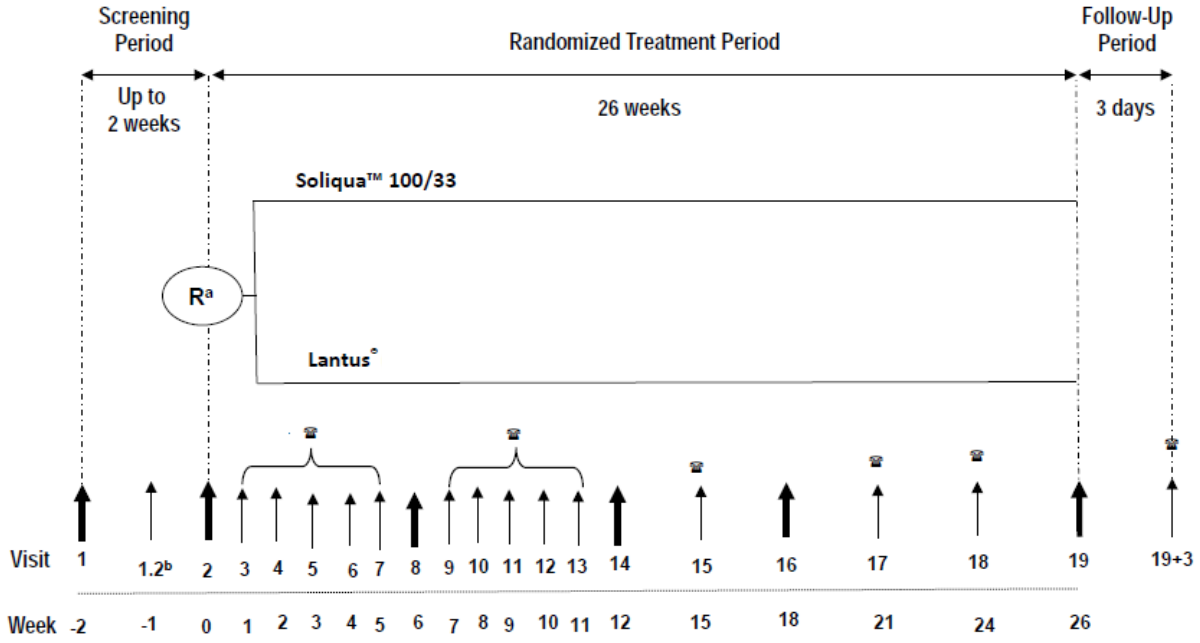
1.2.3 Other objectives

- To assess the effects of Soliqua 100/33 versus Lantus on other efficacy parameters to Week 26 for the selected endpoint 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.

1.3 DETERMINATION OF SAMPLE SIZE

Due to difficulty in recruitment, it has been decided to terminate the trial early, leading to a total sample size of 240 patients (120 per treatment), for which efficacy and safety of Soliqua 100/33 and Lantus will be evaluated using descriptive statistics.

1.4 STUDY PLAN



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, (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

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
01	18-Dec-2017	Removal of extension	Removal of all analysis related to the extension phase
		secondary/other efficacy endpoints	Order of secondary efficacy endpoint testing hierarchy was changed according to the current list of secondary efficacy endpoints.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Table 2 – Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
This version		FDA statistical comments	Safety analysis added: AEs and AESIs summarized over the whole on-study period (on-treatment and post-treatment)
This version		sponsor strategic decision of trial early termination	Changes on sample size and efficacy endpoint analyses
This version			Minor changes in lab test

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

The endpoints listed in this section correspond to the originally planned endpoints collected per protocol. Only the critical endpoints will be analyzed with more details in Section 2.4.

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value prior to the first dose administration of investigational medicinal product (IMP) or the last available value on or before the date of randomization if not treated with IMP.

All baseline safety parameters are presented along with the summary statistics in the safety section (Section 2.4.5). Baseline efficacy parameters are provided as part of the baseline characteristics, in addition to efficacy summaries in the efficacy section (Section 2.4.4).

Demographic characteristics

Demographic characteristics to be summarized are:

- Age (years) derived as: (Date of informed – Date of birth)/365.25,
- Age categories (<50, ≥50 to <65, ≥65 to < 75, ≥75 years),
- Gender (Male, Female),
- Self-reported ethnicity/race (Hispanics of any race, non-Hispanic black/African Americans, and non-Hispanic Asians)),
- HbA1c (%) at Screening,
- FPG at screening,
- Body weight at screening,
- BMI at screening,
- Randomization strata of HbA1c (<8.5%, ≥8.5%) at Screening,
- Randomization strata of background use of SGLT-2 inhibitors (yes, no) at Screening,
- Randomization strata of background use of sulfonylureas (yes, no) at Screening,
- Baseline body mass index (BMI) (kg/m^2) derived as: (Weight in kg)/(Height in meters)^2,
- Baseline BMI categories (<30, ≥30 kg/m^2),

Medical or surgical history

Medical history and medical findings include:

- Medical or surgical history,
- Family allergy history,
- Diabetes history information,
- Diabetes complication history,
- Alcohol habits,
- Tobacco smoking habits.

Medical and surgical history will be coded to a "lower level term (LLT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)", and associated primary "system organ class (SOC)" using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Diabetes history includes:

Duration of diabetes (years) derived as: (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25,

- Duration of diabetes categories: (<10, ≥10 years)
- Age at onset of diabetes (years) derived as: Year of diagnosis of diabetes – Year of birth,
- Type of OADs at Screening
- Type of basal insulin at screening
- History of gestational diabetes (Yes, No)
- Baseline diabetic complications (Yes, No to Diabetic retinopathy, Diabetic neuropathy, and Diabetic nephropathy)
- eGFR at screening (mL/min/1.73m^2),
- eGFR categories at screening (<15 mL/min/1.73m^2 [End stage renal disease], ≥15 to <30 mL/min/1.73m^2 [Severe decrease in GFR], ≥30 to <60 mL/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73m^2 [Normal]).

2.1.2 Prior or concomitant medications

All medications taken within 6 months before the screening visit and until the end of the study are to be reported in the electronic case report form (eCRF).

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

- Prior medications are those the patient used prior to first administration of IMP. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the 1st administration of IMP to the date of last administration + 3 days. A given medication can be classified both as a prior medication and as a concomitant medication.
- Post-treatment medications are those the patient took (continued or initiated) in the period running from the 4th day after the last administration of IMP up to the end of the study.

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.

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 (e.g., 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 hyperglycemia will be considered rescue therapy.
- Systemic (i.e., 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.

2.1.3 Efficacy endpoints

All efficacy measurements collected during the study will be considered for analyses, including those obtained after IMP discontinuation or introduction of rescue therapy. Patients requiring rescue are identified as those with the reason for treatment ticked "rescue therapy" in e-CRF "Medication" page.

HbA1c, 2-hour PPG, FPG, glucose excursions are measured/calculated in a central laboratory (see study flowchart in Appendix C). Body weight, SBP and DBP are measured at on-site visits by the investigator or at the local testing center for subjects enrolled in the virtual sites. Efficacy variables will be summarized in both standard international units and conventional units when applicable.

Standardized meal test

A subset of 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.

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.

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.

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

Observation period

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.

2.1.3.1 Primary efficacy endpoint(s)

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 study flow chart 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.

2.1.3.2 Secondary efficacy endpoint(s)

- 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

2.1.3.3 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

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events, hypoglycemia, and other safety information, such as clinical laboratory data, and vital signs, etc.

Observation period

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 (inclusive) and the first injection of IMP (exclusive),
- The on-treatment period is defined as the time from the first injection of IMP (inclusive) 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).

2.1.4.1 Hypoglycemia

Hypoglycemia will be identified as events recorded on the dedicated e-CRF "Hypoglycemic event information" page, and will be categorized as follows (see study protocol for further details):

Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose 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.

Severe hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Countermeasure Administration", ticked the option "Subject was Not Capable of Treating Self and Required Assistance", and
- To the question "Were Symptoms Present", ticked "Yes".

Documented hypoglycemia with plasma glucose cut-off of≤70 mg/dL (3.9 mmol/L)

Documented hypoglycemia with plasma glucose cut-off of ≤70 mg/dL (3.9 mmol/L) is any hypoglycemia documented by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L); and is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Any Hypoglycemic Events Experienced", ticked "Yes", and
- With a plasma glucose value before countermeasure ≤70 mg/dL (3.9 mmol/L).

Documented hypoglycemia with plasma glucose cut-off of<54 mg/dL (3.0 mmol/L)

Documented hypoglycemia with plasma glucose cut-off of <54 mg/dL (3.0 mmol/L) is any hypoglycemia documented by a measured plasma glucose concentration of <54 mg/dL (3.0 mmol/L); and is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Any Hypoglycemic Events Experienced", ticked "Yes", and
- With a plasma glucose value before countermeasure <54 mg/dL (3.0 mmol/L).

Pseudo hypoglycemia

Pseudo hypoglycemia 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).

Pseudo hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Countermeasure Administration", Do NOT tick the option "Subject was Not Capable of Treating Self and Required Assistance"
- To the question "Were Symptoms Present", ticked "Yes", and
- With a plasma glucose value before countermeasure >70 mg/dL (3.9 mmol/L).

Probable symptomatic hypoglycemia

Probable symptomatic hypoglycemia is 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)), i.e., symptoms treated with oral carbohydrate without a test of plasma glucose.

Probable symptomatic hypoglycemia is identified in e-CRF "Hypoglycemic event" page as those documented as,

- To the question "Countermeasure Administration", the option "Subject was Not Capable of Treating Self and Required Assistance" not ticked, and
- To the question "Were Symptoms Present", ticked "Yes", and
- With no plasma glucose value before countermeasure, and
- To the question "Did this countermeasure lead a significant improvement or prompt recovery?" ticked "Yes".

Any hypoglycemic event fulfilling the criteria of a SAE or leading to unconsciousness, coma, or seizure will also be recorded as a SAE. Only hypoglycemia events fulfilling the criteria of an SAE will also be documented on AE and SAE complementary forms in the eCRF.

2.1.4.2 Adverse events variables

Adverse event observation period

- 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).

All adverse events (including SAE, AESI) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

The occurrence of adverse events (including SAE and AESI) will be recorded from the time of signed informed consent until the end of the study or the resolution/stabilization of all SAE and AESI.

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

AESI are listed below:

- ALT >3 x ULN;
- Serious allergic/hypersensitivity reactions;
- Pregnancy occurring in a female patient administered IMP/NIMP;
- Symptomatic overdose of IMP/NIMP

Table 3 - Criteria for AESI

AE Grouping	Criteria
AESI	
Serious allergic/hypersensitivity reactions	eCRF form "Hypersensitivity/Allergic"
Pregnancy	eCRF form "Pregnancy"
Symptomatic overdose	"Overdose of IMP" or "Overdose of NIMP" checked and "Symptomatic overdose" checked in eCRF form "Overdose"
ALT increase > 3X ULN	eCRF form "ALT increase"

2.1.4.3 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death post-study: deaths occurring after the end of the study

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values will be summarized in both standard international units and conventional units when applicable.

Blood samples for clinical laboratories will be taken at designated visits (see study flowchart in Appendix C). The following laboratory data will be measured at a central laboratory:

- Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes and platelets.
- Clinical chemistry: AST, ALT, ALP, total bilirubin (if >ULN, then the direct and indirect sub-fractions must be measured), creatinine, uric acid, sodium, potassium

Urine samples will be collected at designated visits (see study flowchart in Appendix C). Urinalysis tests will include pH, glucose, ketones, leukocytes, blood/hemoglobin, and protein.

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

Vital signs include: height, weight, BMI, heart rate (HR), systolic and diastolic blood pressure, (see study flowchart in Appendix C for designated visits). They will be performed after the patient has been seated for at least 5 minutes. Blood pressure and HR will be assessed 3 times with at least 1 minute between each measurement following the 5-minute rest period. The mean of the 3 measurements will be analyzed for each vital sign variable (HR, SBP, and DBP).

2.1.5 Pharmacokinetic variables

N/A.

2.1.6 Pharmacodynamic/genomics endpoints

N/A.

2.1.7 Quality-of-life endpoints

The schedule of the following quality of life endpoints are specified in the study flowchart in Appendix C. The sample questionnaires can be found in the study protocol.

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

2.1.7.1 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 study schedules.

The TRIM-D questionnaire 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 (1).

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).

2.1.7.2 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 the question "Overall, how effective has the treatment been in controlling your diabetes, since the start of study medication?" at Week 26. Physician-rated global treatment effectiveness evaluation will be collected in eCRF, and patient-rated global treatment effectiveness evaluation will be collected in the hand-held electronic device.

2.1.8 Health economic endpoints

N/A.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as all patients who signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary tables:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who have completed the study treatment as scheduled
- Patients who discontinued the study treatment, and the reasons for study 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.
- Patients who have completed the study/ follow up as scheduled
- Patients who discontinued the study /follow up, and the reasons for study discontinuation
- Status at last study contact

For screened, screen failure, and nonrandomized but treated patients, percentages will be calculated using the number of screened patients as the denominator. All other categories of patients will be presented by treatment group and the percentages will be calculated using the number of randomized patients within each treatment group as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group.

A summary of the distribution of patients by region and ethnicity/race will also be provided (overall number of patients screened, randomized, and treated, as well as number of patients randomized, discontinued from study treatment, and discontinued from study for each treatment group).

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. The patients that are randomized and not treated as randomized will be part of efficacy and safety analyses. Patients randomized but not treated will be included in efficacy analysis. Safety data of patients treated but not randomized will be reported separately.

All important deviations including randomization and drug-dispensing irregularities will be summarized in tables giving numbers and percentages of deviations by randomized treatment group.

Additionally, the analysis populations for safety and efficacy will be summarized in a table by number of patients in the randomized population.

- Efficacy population: intent-to-treat (ITT) population
- Safety population

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

Patients who are dispensed study drug without calling the IRT or before calling the IRT are considered nonrandomized patients. They are excluded from any population for analysis, including safety. However, if these patients experienced any significant safety event, they would be documented separately in the clinical study report.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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.

2.3.1 Efficacy populations

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.

2.3.2 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 (i.e., all study dates recorded as no medication taken) that patients have not taken IMP.

2.4 STATISTICAL METHODS

Due to early termination of the trial with limited sample size, analyses described in this section will only be performed if sufficient data is available.

2.4.1 Demographics and baseline characteristics

In general, descriptive statistics of quantitative efficacy and safety endpoints (result and change from baseline) by scheduled visit will be provided on observed cases (OC), i.e., only including patients having a non-missing assessment at a specific visit.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Summaries for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall (pooled across treatment groups) using descriptive statistics.

P-values on the treatment difference for the demographic and baseline characteristic data will not be calculated.

In general, no specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety/efficacy analysis.

2.4.2 Prior or concomitant medications

The concomitant and posttreatment medications will be presented in the randomized population for each treatment group using counts and percentages. No statistical test for the between-group difference will be performed.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). A given medication may be classified in more than 1 ATC class. All ATC codes corresponding to a medication will be summarized, and a patient will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore a patient may be counted several times for the same medication.

Concomitant and post-treatment medications will be presented by anatomic and therapeutic categories and sorted by decreasing frequency of ATC based on the incidence in the Soliqua 100/33 group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Prior, concomitant and posttreatment antidiabetic medications classified as antidiabetic insulin therapy and antidiabetic non-insulin therapy will be presented separately.

- The antidiabetic insulin therapy will be summarized by pre-defined classification of
  - Basal insulin
  - Short-acting insulin
  - Pre-mixed insulin

  and standardized medication name.
- The antidiabetic non-insulin therapy will be summarized by pre-defined classification of
  - Biguanides
  - Sulfonylurea
  - Glinides
  - Thiazolidinedione
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - GLP1-RA
  - Alpha-glucosidase inhibitors
  - Other

and standardized medication name.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as last dose date of IMP – first dose date of IMP + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number of patients exposed, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- 1 to 28 days,
- 29 to 56 days,
- 57 to 84 days,
- 85 to 126 days,
- 127 to 168 days
- 169 to 175 days
- 176 to 182 days
- >182 days

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

Number and percentages of patients by final dose at the end of the treatment will also be presented by each treatment group.

2.4.3.2 Compliance

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.

Percentage of compliance for a patient will be defined as the number of days that the patient was compliant divided by the total number of days that the patient was planned to take during the treatment period from the first date to the last date of IMP administration.

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

Above-planned dosing percentage for a patient will be defined as the number of days that the patient took a higher dose than planned divided by the total number of days that the patient was planned to take during the treatment period.

Under-planned dosing percentage for a patient will be defined as the number of days that the patient took a lower dose than planned divided by the total number of days that the patient was planned to take during the treatment period.

Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). In addition, the percentage of patients who have <60%, ≥60 to <80%, ≥80 to ≤100%, and >100% compliance will be summarized by treatment group.

Cases of overdose (see study protocol for further details) will constitute AEs/SAEs and be analyzed as such.

2.4.4 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population using the efficacy assessments collected during the study, including those obtained after IMP discontinuation or introduction of rescue therapy, unless otherwise specified.

The primary efficacy endpoint will only be summarized by descriptive statistics without formal statistical testing due to limited sample size and insufficient power.

Missing data for efficacy analyses is identified through steps described in Section 2.5.3.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Summaries of the primary efficacy endpoint (change from baseline to Week 26 in HbA1c) will be performed using observed cases for each treatment group based on the ITT population, using HbA1c values obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or rescue medication use. The summary will include the number of observations, mean, SD, standard error (SE), minimum, median, and maximum.

Summary statistics at scheduled visits

Summary statistics (for screening value, baseline value, observed post-baseline value and its changes from baseline) at scheduled visits (using observed cases) will be provided for each

treatment group, both for the overall population and separately for each ethnicity/race subgroup. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE) at each of the scheduled visits.

2.4.4.2 Analyses of secondary efficacy endpoints

Analyses of the secondary efficacy endpoints will be performed using the ITT population for all patients and, separately, by ethnicity/race subgroup. The originally collected change from baseline to Week 26 in 2-hour glucose excursion will no longer be considered critical and will not be analyzed.

For all continuous secondary endpoints except 2-hour glucose excursion, summary statistics at scheduled visits and the changes from baseline will be provided using observed cases for each treatment group, both for the overall population and separately for each ethnicity/race subgroup. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (± SE) and mean changes from Baseline (± SE) at each of the scheduled visits. For percentage (%) of patients achieving the HbA1c target of <7% at scheduled visits, the proportion in each treatment group will be provided. All values at scheduled visits 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 scheduled visits, patients will be treated as failures (non-responders).

2.4.4.3 Multiplicity issues

Not applicable since no formal testing will be performed.

2.4.4.4 Additional efficacy analysis

Analyses of other efficacy endpoints 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, both for the overall population and separately for each ethnicity/race subgroup.

All other efficacy variables originally collected, except the change from baseline to Week 12 in HbA1c and percentage of patients requiring rescue therapy by Week 26, will no longer be considered critical and will not be analyzed. The analysis of other endpoints (see Section 2.1.3.3) will be descriptive with no formal testing.

The number (%) of patients who used rescue therapy and a KM curve for the time to first rescue therapy will be provided by treatment group. A list of patients who used rescue therapy will also be provided. Time to rescue will be defined as the number of days from the first administration of IMP until the start date of any rescue medication. Patients who did not take any rescue medication

during the 26-week treatment period will be considered as censored observations. The censoring time will be the last administration date (e-CRF "Treatment Status Library" page), or the end date of the study (e-CRF "Completion of End of Study/Follow-up" page) if the last administration date is not available, or the last contact date if the last administration date and end date of the study are not available.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group, for both the overall population and separately for each ethnic/race subgroup, for the 26-week randomized treatment period, unless specified otherwise.

All safety analyses will be performed on the safety population using the following common rules:

The "observation period" defined in Section 2.1.4 is applicable in all safety analyses for the classification of AEs, determination of treatment-emergent Potentially Clinically Significant Abnormality (PCSA) values and the last on-treatment value for the laboratory, vital sign and ECG.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., exposed but not randomized) will be listed separately
- The baseline value is defined as the last available value before the first dose of IMP
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG. PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment emergent PCSA percentage
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population.
- For laboratory parameters cited in the protocol as efficacy endpoints (including HbA1c and plasma glucose etc.), PCSA summaries will not be provided. These parameters will be summarized in Section 2.4.4.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group for the entire 26-week treatment period only. Summaries will include the last on-treatment value. The last on-treatment value is commonly defined as the value collected at the same day/time of the last administration of IMP. If this value is

missing, this last on-treatment value will be the closet value prior to the last dose administration of IMP during the entire 26-week treatment period.

- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus Lantus and their 95% confidence intervals may be provided, if relevant

2.4.5.1 Hypoglycemia

Analyses of hypoglycemia will be performed on the TEAE period as defined in Section 2.1.4. Hypoglycemia will be classified as severe hypoglycemia, documented hypoglycemia (blood glucose ≤70 mg/dL and <54 mg/dL), probable symptomatic hypoglycemia or pseudo hypoglycemia.

The number (%) of patients with at least 1hypoglycemia, severe hypoglycemia and documented hypoglycemia (blood glucose ≤70 mg/dL and <54 mg/dL), probable symptomatic hypoglycemia or pseudo hypoglycemia will be summarized respectively by treatment group during the TEAE period, as well as the incidence rate in patient years. Two types of incidence rates will be presented: the number of patients with at least 1 event per patient-year (calculated as the number of patients with at least 1 event / total exposure in patient-year), and the number of events per patient-year (calculated as the total number of events / total exposure in patient-years). Note: here exposure (in days) is the duration of TEAE period, i.e., duration of IMP treatment in days +1 (see Section 2.1.4).

A KM curve will also be provided by treatment group for the time to first severe hypoglycemia or documented hypoglycemia during the TEAE period for the entire 26-week treatment period only.

A listing of patients for all events reported on the dedicated e-CRF “Hypoglycemic event information” page will be provided with each category flagged (i.e., severe hypoglycemia, documented hypoglycemia, probable symptomatic hypoglycemia and pseudo hypoglycemia).

2.4.5.2 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment andpost-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will be presented by SOC, HLGT, HLT, and PT, sorted by the internationally agreed order for SOCs and alphabetic order for HLGT, HLT and PT within a SOC, the number (n) and percentage (%) of patients experiencing an adverse event. 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.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by primary SOC and PT (sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs in the Soliqua 100/33 group) will define the presentation order for all other similar tables unless otherwise specified. In case of equal frequency regarding PTs, alphabetical order will be used.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated during the 26-week randomized treatment period for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- All treatment-emergent adverse events by primary SOC, showing number (%) of patients with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary system organ class
- All adverse events for the whole on-study period (on-treatment and post-treatment periods) by primary SOC, showing number (%) of patients with at least 1 adverse event during the on-study period, sorted by internationally agreed order of primary system organ class
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT in the Soliqua 100/33 group
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC in the Soliqua 100/33 group. This sorting order will be applied to all other similar tables, unless otherwise specified

- All treatment-emergent adverse events regardless of relationship and related to IMP by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (i.e., mild, moderate, or severe), sorted by the sorting order defined above
- Common TEAEs (PTs with an incidence ≥1% in any treatment group) by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of SOCs. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.
- Common TEAEs (PTs with an incidence ≥1% in any treatment group) will be provided as appropriate by primary SOC, HLGT, HLT, and PT and by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years of age), race (White, Black or African American, Asian, other). SOC will be sorted by internationally agreed order and the other levels (HLGT, HLT, PT) in alphabetic order.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

Analysis of adverse events of special interest

- Serious allergic/hypersensitivity reactions, pregnancy and overdose for the combined on-treatment and post-treatment period will be included in overall AE summaries if any are reported. ALT increase >3 x ULN for the TEAE period is included in laboratory PCSA summary and listed in the PCSA listing which will include both the on-treatment and post-treatment periods.

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.

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the Soliqua 100/33 group
- All posttreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC in the Soliqua 100/33 group

Listings

Supportive AE listings will be provided for all AEs, SAEs, AEs leading to treatment discontinuation and/or death, and EOSI as appropriate. Listing of all AEs, SAEs and AEs leading to treatment discontinuation and/or death, sorted by treatment, patient identification and onset date, will include at least the following information: treatment, patient identification, country, age, gender, race, BMI, primary SOC, PT, reported term, onset date, study day (relative day to the start date of IMP treatment), AE duration, duration of exposure, intensity, corrective treatment, action taken with IMP, date of treatment discontinuation (if relevant), relationship to IMP, outcome, date of death (if any), seriousness, seriousness criteria, and AE status (“Pre” for a pre-treatment AE; “T” for a TEAE; and “Post” for an on-study post-treatment AE).

2.4.5.3 Deaths

The following summaries of deaths will be generated.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study)
- Deaths in nonrandomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.

2.4.5.4 Analyses of laboratory variables

Laboratory parameters will be taken at baseline and summarized as part of baseline characteristics.

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables) will be calculated by treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

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

All measurements collected during the TEAE period, including values from unscheduled visits, will be considered for the PCSA summaries. These summaries will include patients in the safety population who have at least 1 assessment performed during the TEAE period. When a PCSA definition involves a change from baseline value, patients must also have a baseline value to be included in the summaries, and when required by the definition of the abnormality, patients must also have available laboratory normal ranges.

A listing of patients with at least 1 post-baseline PCSA during the on-treatment and post-treatment period (or out of normal range when no PCSA criterion is defined) will be provided which will display the entire patients' profile across time for all parameters belonging to the corresponding biological function. Individual data listings will include the following flags when applicable:

- Baseline values will be flagged "B".
- Normal laboratory ranges, available for most laboratory parameters, will be identified as ULN and LLN. Baseline, last on-treatment value, and individual data will be flagged "L" if the value is below the LLN and will be flagged "H" if it is above the ULN.
- Laboratory PCSA criteria will be used for the corresponding laboratory parameters. Values reaching a PCSA limit will be flagged (+, ++, -, or -- depending upon the direction and level of the abnormality). Flags for WBC and differential counts will be determined using data expressed in international units.

For parameters whose PCSA criteria are multiples of the ULN, the parameter's value will also be expressed as a multiple of the ULN in the individual data provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group (only if a tabulation summary is necessary).

Listing of possible Hy's law cases identified by treatment group (e.g., patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters (if available): conjugated bilirubin and prothrombin time/international normalized ratio, creatine phosphokinase, serum creatinine, complete blood count.

2.4.5.5 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of heart rate, temperature and respiratory rate (observed values, or mean of observed values, and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment value) by treatment group.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group for SBP, DBP and HR. All measurements collected during the TEAE period, including values from unscheduled visits, will be considered for the PCSA summaries. The summaries will include patients in the safety population who have at least 1 assessment performed during the TEAE period. When a PCSA definition involves a change from baseline value, patients must also have a baseline value to be included in the summaries.

A listing of patients with at least 1 post-baseline PCSA will be provided and will display the patient's profile over time of all vital sign parameters. Individual data listings will include the following flags:

- Baseline values will be flagged "B",
- Parameter values reaching a PCSA limit will be flagged (+, or - depending of the direction).

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

N/A.

2.4.7 Analyses of patient reported outcome variables

The data originally planned were no longer considered to be critical and evaluations will not be performed.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

HbA1c

The formula to convert HbA1c from Diabetes Control and Complications Trial (DCCT) aligned value to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized value is,

IFCC-HbA1c (mmol/mol) = [DCCT-HbA1c (%) - 2.15] x 10.929.

Renal function formulas

The estimated GFR (mL/min/1.73 m^2) will be calculated using the 4 variable Modification of Diet in Renal Disease (MDRD) formula:

Standard unit: eGFR (mL/min/1.73 m^2) = 175 x [Serum Creatinine (µmol/L)/88.4] $^{-1.154}$ x Age (year) $^{-0.203}$ x 1.212 (if Black) x 0.742 (if Female)

Conventional unit: eGFR (mL/min/1.73 m^2) = 175 x Serum Creatinine (mg/dL) $^{-1.154}$ x Age (year) $^{-0.203}$ x 1.212 (if Black) x 0.742 (if Female)

2.5.2 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Derived variables will be considered missing if any of the original variables required to calculate them are missing. For example, if either a baseline assessment or an endpoint assessment is missing for a particular patient, then change from baseline at endpoint will be missing. Depending upon the assessment, analyses may not include all patients in the analysis population, because certain patients in the intended population may have missing data.

Incomplete date of first administration of IMP

Date/time of first administration is the first non-missing start date/time of IMP.

For patients who are randomized and dispensed a treatment kit but who are lost to follow-up just after Visit 2, the date of first administration will be imputed using the date of randomization. When a patient is randomized but not exposed, “Not taken” should be ticked in the e-CRF “First dose IMP” module.

Handling of computation of treatment duration if IMP end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the e-CRF “Treatment status library” page. If this date is missing, the exposure duration should be left as missing.

The last dose administration should be clearly identified in the case report form and should not be approximated by the last returned package date.

In the case of subjects being exposed to more than 1 IMPs, the missing end of treatment date for one IMP could be imputed as the day before the non-missing first administration date of the next IMP date.

Handling of medication missing/partial dates

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

Handling of adverse events/hypoglycemia with missing or partial date/time of onset

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

Handling of adverse events/hypoglycemia when date and time of first IMP administration is missing

When the date and time of the first IMP administration is missing, the day of randomization should be considered as the start date of TEAE period (see Section 2.1.4). The exposure duration should be kept as missing.

Handling of adverse events/hypoglycemia when IMP end of treatment date is missing

For the purpose of defining TEAE period, the date of the last administration of IMP is equal to the date of the last administration reported on the eCRF "Treatment Status Library" page.

If the date of last administration reported on the eCRF "Treatment Status Library" page is

- Partially missing, it will be imputed with a date as late as possible before or on the date of last available information on eCRF "Completion of End of Study/Follow-up".
- Completely missing, it will be imputed with the date of last available information on eCRF "Completion of End of Study/Follow-up" page.

If the date of last available information on eCRF "Completion of End of Study/Follow-up" page is

- Partially missing, it will be imputed with a date as late as possible.
- Completely missing, all adverse events occurred on or after the first administration of IMP will be considered as treatment emergent adverse events.

Handling of missing assessment of relationship of adverse events to IMP

If the assessment of the relationship to IMP is missing, the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity/grades of adverse events

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Linked adverse events that worsened or became serious

An AE that worsened or became serious will have a separate record in the data from the original event record with an AE identification number that links the new record to the original record. An AE that worsened or became serious will be considered a new recurring AE in the summary of recurrent events or in the summary of events by time intervals.

Handling of missing data for continuous efficacy endpoints

Please see Section 2.4.4.1 and Section 2.5.3.

2.5.3 Windows for time points

The following steps will decide how the scheduled and/or unscheduled visits will be used in the analyses on efficacy variables and the by-visit summaries for safety variables.

Step 1 A scheduled measurement will be used if it is available; otherwise, an unscheduled measurement (including the end of treatment/study visit for those prematurely discontinued) will be used if it happens to be on the same date as the date of the scheduled visit.

Step 2 After Step 1, if there are still no measurement for a given parameter at a scheduled visit, the analysis window below (Table 4) will be applied to re-allocate a post-baseline unscheduled measurement to a scheduled measurement.

Table 4 - Analyses window definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 6 (Visit 6)	42	1 to 83
Week 12 (Visit 14)	84	84 to 104
Week 18 (Visit 16)	126	105 to 153
Week 26 (Visit 19)	182	154 to 195

Study days are calculated from the day of first administration of IMP; the day of first administration of IMP (or the day of randomization if not exposed) is Day 1.

After applying the above time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. In case of equality, the last measurement will be used. Re-allocated scheduled visits (i.e., visit numbers) should be sequential if ordered by the date of measurement.

After Step 2, if there are still no measurement for a given parameter at a scheduled visit, data is considered missing for efficacy analyses, where multiple imputation would be applied as appropriately as described in Section 2.4.4.

For endpoints where measurements were only taken at baseline and Week 26, post-baseline measurement that is closest to the Week 26 target day will be used for Week 26.

Reference day

The reference day for the calculation of extent of exposure, time to onset, and relative days will be the day of the first administration of IMP or the day of randomization if not exposed to IMP, denoted as Day 1.

Baseline definition for efficacy/safety data

For the safety analyses, the baseline for a given parameter is defined as the last available measurement including unscheduled assessments, assessed prior to the first administration of IMP. For the efficacy analyses, the baseline for a given parameter is defined as the last available measurement including unscheduled assessments, assessed prior to the first administration of IMP or the last available value before randomization if not treated with IMP.

Summary statistics by visit for continuous efficacy endpoints

Summary statistics (number, mean, SD, SE, minimum, median, maximum) of continuous efficacy endpoints (observed data and change from baseline) will be provided at scheduled visits as per protocol. Summaries showing data by visit will be presented according to the visit number (or re-allocated visit number) and labeled with the targeted approximate day/week.

Last on-treatment value for laboratory variables and vital signs

The last on-treatment value is the final measurement assessed during the treatment epoch, regardless of the introduction of rescue therapy, including measurements at unscheduled visits.

Display of safety data by visit (laboratory variables and vital signs)

Descriptive statistics (number, mean, SD, minimum, median, maximum) of quantitative laboratory variables and vital signs (observed data and change from baseline) during the TEAE period will be provided at scheduled visits. In addition, these summaries will also include a row for the 'last value on-treatment' to describe the last available on-treatment value (see above). Summaries showing data by visit will be presented according to the visit number (or re-allocated visit number) and labeled with the targeted approximate day/week.

As specified in the study protocol, laboratory data from scheduled visits are reported by central laboratories. The local results will not be used in the efficacy analyses or in the definition of baseline for both safety and efficacy analyses. In the safety analyses, local results will only be used in the PCSA summary if they are accompanied by a local laboratory normal range.

When a patient has more than 1 measurement from the central laboratory for the same laboratory parameter on the same date, the average of the measurements will be used. For the same laboratory parameter, if a patient has more than 1 measurement on different dates for the same scheduled visit, the value closest to the date of the visit will be used for the scheduled visit. When the values for the same scheduled visit are equidistant, the last value should be used for the scheduled visit. Similar rules will be applicable to a patient who has more than 1 set of measurements for the same vital sign parameter (i.e., SBP, DBP, or HR) on the same date.

26-week randomized treatment period

The 26-week randomized treatment period is the time from first administration of IMP to the last administration of IMP on or before Visit 19/Week 26 (or Day 182 if Visit 19/Week 26 date is missing). This is for defining EOT status at Week 26 and analyzing selected efficacy parameters during the 26-week randomized core treatment period.

TEAE period for the 26-week randomized treatment period

The TEAE period for 26-week randomized treatment period is (1) the time from the first administration of the IMP up to 10 days (1 day for hypoglycemia) after the last administration of IMP if the patient discontinued treatment on or before Visit 19/Week 26 (or Day 182 if Visit 19/Week 26 date is missing), or (2) the time from the first administration of the IMP to the administration at Visit 19/Week 26 (or Day 182 if Visit 19/Week 26 date is missing) if the patient remained treated beyond Visit 19/Week 26. This is for the purpose of safety analyses during the 26-week randomized treatment period.

2.5.4 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and etc. but will be used for computation of baseline, the last on-treatment value, PCSAs, and the shift summaries for safety or efficacy. They will be included in the by-visit summaries if they are re-allocated to scheduled visits.

2.5.5 Pooling of centers for statistical analyses

Center or pooling of centers is not planned and will not be included in the statistical models for efficacy analyses.

2.5.6 Statistical technical issues

N/A.

3 INTERIM ANALYSIS

No formal interim analysis is planned for this study.

4 DATABASE LOCK

The database is planned to be locked approximately 8 weeks after the last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS® version 9.2 or higher.

6 REFERENCES

1. Savre I, Mapi Research Trust. TRIM-D Treatment Related Impact Measure-Diabetes. Infomation booklet. 1st ed. Hojbjerre L, Novo Nordisk. France. Mapi Research Trust;c2013. 41p.

7 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA	Comments
Clinical Chemistry	
By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA	Comments
>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurements.
>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA	Comments
<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
>408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
≥17 mmol/L	
<80 mmol/L >115 mmol/L	
≤129 mmol/L ≥160 mmol/L	
<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
≥7.74 mmol/L	Threshold for therapeutic intervention.
≥4.6 mmol/L	Threshold for therapeutic intervention.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA	Comments
≥3 ULN	
≥3 ULN	
≤3.9 mmol/L and <LLN	ADA May 2005.
≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
>8%	
≤25 g/L	
>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology	
<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black)	Increase in WBC: not relevant.
≥16.0 Giga/L	To be interpreted only if no differential count available.
>4.0 Giga/L	
<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
>0.7 Giga/L	
>0.1 Giga/L	
>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA	Comments
≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis	
≤4.6 ≥8	
Vital signs	
≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA	Comments
≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
≤-20 mmHg ≤-10 mmHg	
≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA		Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	Categories are cumulative
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
PR	>200 ms	Categories are cumulative
	>200 ms and increase from baseline ≥25%	
	> 220 ms	
	>220 ms and increase from baseline ≥25%	
	> 240 ms	
	> 240 ms and increase from baseline ≥25%	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 May 21, 2014)

PCSA		Comments
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
QT	>500 ms	
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix B Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
HbA1c: Change from baseline at Week 26, (Soliqua 100/33 vs. Lantus)	ITT	Summary statistics only			Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit.
Secondary endpoints					
Proportion of patients with HbA1c target of <7% at Week 26; 2-hour PPG, daily insulin glargine dose and body weight: Change from Baseline to Week 26;	ITT			.	Summary statistics for observed values and changes from baseline by visit. Graphical presentations for mean changes from baseline (±SE) and mean values (±SE) by visit.
		Summary statistics only			
Other endpoints					
HbA1c change from baseline to Week 12;	ITT	Summary statistics only		No	Summary statistics for observed values and changes from baseline by visit. . For patients requiring rescue treatment: KM plot; List of patients rescued
Proportion of patients requiring rescue treatment by Week 26	ITT				

SAFETY ANALYSES

Endpoint	Analysis Population	Primary analysis	Supportive Analysis	Subgroup analysis	Other analyses
Hypoglycemia	Safety	Follow safety guidelines Number (%) of patients with any hypoglycemia, severe hypoglycemia, documented hypoglycemia, pseudo hypoglycemia and probable symptomatic hypoglycemia during TEAE period, and summary of frequency and incidence rates in 100 patient-years.	No	No	KM plot time to first event of severe hypoglycemia or documented hypoglycemia
Adverse Events	Safety	Follow safety guidelines	No	Common TEAEs by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 years of age), race (White, Black or African American, Asian, other)	No
Clinical laboratory data	Safety	Follow safety guidelines	Descriptive	No	No
Vital signs	Safety	Follow safety guidelines	Descriptive	No	No

Appendix C Study flow chart

STUDY FLOW CHART

Study Period	Screening		Open-label Randomized Treatment																		Follow-Up Visit
VISIT[a]	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
				☎	☎	☎	☎	☎		☎	☎	☎	☎	☎		☎		☎	☎		☎
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		

Study Period	Screening		Open-label Randomized Treatment																	Follow-Up Visit
VISIT[a]	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
				☎	☎	☎	☎	☎		☎	☎	☎	☎	☎		☎		☎	☎		☎
WEEK	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	26	26+3 days
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	
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		
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																				

Study Period	Screening		Open-label Randomized Treatment																	Follow-Up Visit
VISIT[a]	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
				☎	☎	☎	☎	☎		☎	☎	☎	☎	☎		☎		☎	☎		☎
WEEK	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	26	26+3 days
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

a. Screening period duration is of up to 2 weeks (i.e., 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 (i.e., 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=weight (kg)/(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 (i.e., 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.

LPS14860 16.1.9 Statistical Analysis Plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	28-Feb-2019 16:38 GMT+0100
[redacted]	Clinical Approval	09-Apr-2019 03:53 GMT+0200
[redacted]	Clinical Approval	09-Apr-2019 23:39 GMT+0200