NCT05114590

CLINICAL STUDY PROTOCOL
U1111-1261-7399
A 16-Week, Multicenter, Prospective, Open-Label, Single-Arm, Phase 4 Study to Evaluate the Effect of Soliqua™ 100/33 on the Percentage of Time in Range (TIR) from Continuous Glucose Monitoring (CGM) in Insulin-Naïve Patients With Very Uncontrolled Type 2 Diabetes Mellitus
LPS16990

Short Title	Soli-CGM
Sponsor:	Sanofi US Services Inc. 55 Corporate Drive Bridgewater, NJ 08807 USA
Sponsor Contact:	[redacted]
Medical Monitor:	
Version of Protocol:	
Date of Protocol:	18 Aug 2021

CONFIDENTIAL

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

Protocol Approval – Sponsor Signatory

Study Title	A 16-Week, Multicenter, Prospective, Open-Label, Single-Arm, Phase 4 Study to Evaluate the Effect of Soliqua™ 100/33 on the Percentage of Time in Range (TIR) from Continuous Glucose Monitoring (CGM) in Insulin-Naïve Patients With Very Uncontrolled Type 2 Diabetes Mellitus
Short Title	Soli-CGM
Protocol Number	LPS16990
Protocol Date	18 Aug 2021

Protocol accepted and approved by:

Senior Medical Director

[redacted]

Signature Date

Declaration of Investigator

I have read and understood all sections of the protocol titled "A 16-Week, Multicenter, Prospective, Open-Label, Single-Arm, Phase 4 Study to Evaluate the Effect of Soliqua™ 100/33 on the Percentage of Time in Range (TIR) from Continuous Glucose Monitoring (CGM) in Insulin-Naïve Patients With Very Uncontrolled Type 2 Diabetes Mellitus" and the accompanying prescribing information, dated February 2019.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1.0, dated 18 Aug 2021; the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice; and all applicable government regulations. I will not make changes to the protocol before consulting with Sanofi US Services Inc. or implement protocol changes without institutional review board approval except to eliminate an immediate risk to participants. I agree to administer study drug only to participants under my personal supervision or the supervision of a sub-investigator.

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

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Sanofi US Services Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:	LPS16990
Universal Trial Number:	U1111-1261-7399
Title:	A 16-Week, Multicenter, Prospective, Open-Label, Single-Arm, Phase 4 Study to Evaluate the Effect of Soliqua™ 100/33 on the Percentage of Time in Range (TIR) from Continuous Glucose Monitoring (CGM) in Insulin-Naïve Patients With Very Uncontrolled Type 2 Diabetes Mellitus
Short Title	Soli-CGM
Sponsor:	Sanofi US Services Inc. 55 Corporate Drive Bridgewater, NJ 08807 USA
Study Phase:	Phase 4
Study Sites:	US only: Multicenter (Approximate number of sites: 15)
Indication:	Type 2 diabetes mellitus
Rationale:	Soliqua™ 100/33 is a fixed-ratio combination of insulin glargine U100 (100 units/mL) plus lixisenatide (33 µg/mL), a glucagon-like peptide 1 receptor agonist (GLP-1 RA; Soliqua 2019). The combination of a basal insulin and a GLP-1 RA addresses both fasting and postprandial hyperglycemia, thus ensuring more comprehensive glycemic control than basal insulin alone. The efficacy and safety of Soliqua 100/33 has been clearly established in randomized controlled clinical studies. In the LixiLan-O study, the glycated hemoglobin (HbA1c) of patients uncontrolled on oral antidiabetic drugs (OADs) who were treated with Soliqua 100/33 decreased from 8.1% (baseline) to 6.5% (end of study) with the majority (74%) achieving the HbA1c target of <7% (Rosenstock et al 2016). The efficacy of Soliqua 100/33 was also demonstrated by a 2.9% HbA1c reduction from baseline, with 74% of patients achieving an HbA1c of <7%, in a subgroup of patients with type 2 diabetes mellitus (T2DM) with baseline HbA1c ≥9% uncontrolled on OADs from the LixiLan-O study (Davies et al 2019). Similarly, patients uncontrolled on basal insulin in the LixiLan-L study demonstrated an HbA1c reduction from 8.1% to 6.9%, and most (55%) reached their target HbA1c of <7% (Aroda et al 2016). These results were achieved without weight gain and with fewer gastrointestinal (GI) side effects than with lixisenatide alone, likely

due to a more gradual titration of the GLP-1 RA dose (Rosenstock et al 2016; Davies et al 2019).

Continuous glucose monitoring (CGM) provides a more complete picture of glycemic exposure and excursions than self-monitored blood glucose or HbA1c (Danne et al 2017). In the US, use of CGM is becoming mainstream, driven by improved sensor accuracy, convenience, ease of use, cost-effectiveness, and increased reimbursement. Continuous glucose monitoring facilitates improved glycemic control while reducing hypoglycemia risk (Danne et al 2017; Battelino et al 2019) and is rapidly becoming standard of practice for many healthcare providers (HCPs) for management of patients with type 1 diabetes mellitus (T1DM) and insulin-treated T2DM.

Time in range (TIR) is one of the metrics derived from CGM and is increasingly utilized to assess glycemic control. It can correlate with HbA1c values as well as the risk of diabetes-related complications (both microvascular and macrovascular). The International Consensus Report on "clinical targets for CGM interpretation" has identified "TIR" as a metric providing more actionable information than HbA1c and has defined targets for clinical use(Battelino et al 2019). For example, in patients with uncomplicated T2DM whose HbA1c targets are <7%, the recommended TIR (for a target range of 70-180 mg/dL) is >70% of the readings.

Soliqua 100/33 is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (Soliqua 2019). The 2021 Standards of Medical Care in Diabetes from the American Diabetes Association (ADA; ADA 2021a; ADA 2021b) recommends the use of fixed-ratio combinations when the combination of individual components is indicated, such as when a GLP-1 RA is added to basal insulin or vice versa. The ADA 2021 Standards also recommend dual combination therapy in individuals with HbA1c values ≥1.5% from their glycemic target. Correlations of HbA1c and TIR indicate that CGM glucose readings of patients with an HbA1c ≥9% are in range 40% of the time or less, compared with the 70% TIR associated with an HbA1c of 7% (Battelino et al 2019). Although there are currently no studies using CGM measurements to capture glycemic excursions and variability related to Soliqua 100/33, a post hoc analysis demonstrated improvement in all measures of glycemic variability compared with its individual components (eg, lixisenatide or insulin glargine U100), assessed by 7-point blood glucose profiles. These findings were attributable to Soliqua 100/33's complementary mechanisms of action, which

	demonstrate reductions in both fasting and postprandial hyperglycemia (Aronson et al 2019). The current study is intended to replicate these results using CGM to measure TIR and glycemic variability in a patient population with very uncontrolled T2DM (HbA1c ≥9%-13%), who are most likely to benefit from a fixed-ratio combination approach, such as Soliqua 100/33. The primary objective of this study is to demonstrate an improvement in the percentage of TIR from baseline to the end of the study (16 weeks) in insulin-naïve patients with very uncontrolled (HbA1c ≥9%-13%) T2DM on 2+ OADs with or without GLP-1 RAs.
Benefit-Risk Assessment	Soliqua 100/33 has demonstrated superior glycemic efficacy in patients with T2DM uncontrolled on oral therapies, basal insulin, or GLP-1 RA (including weekly GLP-1 RA) with durable efficacy (52 weeks) compared with its individual components (insulin glargine U100 and lixisenatide), and recently premixed insulin analog (BIAsp 30) in those uncontrolled on basal insulin and oral therapies (Rosenstock et al 2021). Additionally, compared with insulin glargine U100 alone, patients on Soliqua 100/33 had weight neutrality with no increase in hypoglycemia events; compared with lixisenatide alone, they experienced fewer GI adverse events (AEs) (Aroda et al 2016; Rosenstock et al 2016; Blonde et al 2019). Soliqua 100/33 has also shown greater HbA1c reduction, less weight gain, and less hypoglycemia compared to a premixed insulin analog (BiAsp 70/30) in individuals not controlled on basal insulin therapy (Rosenstock et al 2021). No new risks have been identified for the population to be included in Study LPS16990. In this study, treatment with Soliqua 100/33 will be consistent with the current US Food and Drug Administration (FDA)-approved label indications (Soliqua 2019). During the titration period, the dose of Soliqua 100/33 will be adjusted upwards or downwards by 2 to 4 units every week, or at the investigator's discretion, based on the participant's blood glucose monitoring results, with the objective of safely attaining a fasting self-measured plasma glucose (SMPG) value of 80 to 100 mg/dL, as well as other glycemic goals, while minimizing the risk of hypoglycemia and hyperglycemia. The duration of the titration period and number of phone contacts to safely meet the study goals will also be at the discretion of the investigator. Therefore, the risk for patients participating in this study and using daily doses of Soliqua 100/33 up to a maximum of 60 units of insulin glargine and 20 µg of lixisenatide is considered acceptable.

All patients enrolled in this study will benefit from medical care and continuous monitoring of their glucose levels.

The important identified risks for Soliqua 100/33 are hypoglycemia or hyperglycemia associated with alterations in the insulin dosing regimen, hypersensitivity reactions, overdose due to medication errors, injection site reactions, and GI AEs, including nausea, diarrhea, and vomiting. This study proposes a titration algorithm with titration targets that will closely follow the US label for Soliqua 100/33(Soliqua 2019), except in instances of hyper- or hypoglycemia, which require specific attention. All study participants will benefit from the safety monitoring planned during site visits as well as during the additional titration phone contacts.

Given the expected improvement of glycemic control and the additional measures to improve diabetes management, the benefits are considered to outweigh any potential risks associated with Soliqua 100/33. Therefore, the benefit-risk ratio for patients participating in Study LPS16990 is considered favorable.

Objectives and Endpoints:

Objectives	Endpoints
To determine the effect of Soliqua 100/33 on indices of glycemic control and variability, as measured via CGM, from baseline to Week 16, in insulin-naïve patients with very uncontrolled (HbA1c ≥9%-13%) T2DM	
Efficacy Objectives	
Primary Objective	**Primary Endpoint**
• To demonstrate that in patients with T2DM failing to achieve glycemic control (HbA1c ≥9%-13%) on their current regimen of 2+ OADs with or without GLP-1 RAs, introduction of Soliqua 100/33 exhibits superiority in terms of time spent in range (70-180 mg/dL) at Week 16 compared with baseline, as measured by CGM	• Change in the percentage of TIR (70-180 mg/dL) from baseline to Week 16

Key Secondary Objectives	**Key Secondary Endpoints**
• To evaluate the impact of Soliqua 100/33 on measures of glycemic control and variability in patients with T2DM	• Change (%) from baseline to Week 16 in coefficient of variation (CV) • Change (mg/dL) from baseline to Week 16 in mean daily blood glucose • Change (mg/dL) from baseline to Week 16 in the maximum postprandial glucose (PPG) exposure in the 4 hours after the breakfast meal • Change (%) from baseline to Week 16 in time above range (TAR; >180 mg/dL)
Secondary Objectives	**Secondary Endpoints**
• To evaluate the impact of Soliqua 100/33 on other measures of glycemic control and variability in patients with T2DM	• Proportion (%) of patients achieving CV <36% • Change (%) from baseline to Week 16 in TIR (70-180 mg/dL) for specific time blocks (6 am-12 pm, 12 pm-6 pm, 6 pm-12 am, and 12 am-6 am) • Proportion (%) of patients achieving Glucose Management Indicator (GMI) <7% and <9% at Week 16 • Change from baseline to Week 16 in the 4-hour PPG area under the concentration versus time curve from 0 to 4 hours (AUC_{0-4h}) after start of the breakfast meal, including time to reach maximum concentration (T_{max}) • Proportion (%) of patients at Week 16 who spend <15 minutes/day at a glucose level <54 mg/dL

Other Efficacy Objectives • To evaluate the impact of Soliqua 100/33 on additional measures of glycemic control and variability in patients with T2DM	**Other Efficacy Endpoints and Analyses** • Change (mg/dL) from baseline to Week 16 in mean of daily difference (MODD) of glucose levels • Change (%) from baseline to Week 16 in TAR (>250 mg/dL) • Change (%) from baseline to Week 16 in time below range (TBR; <70 mg/dL) • Correlation of change in the percentage of TIR (70-180 mg/dL) and least square (LS) mean change in patient-reported outcome (PRO) from baseline to Week 16 • Correlation of percentage of TIR (70-180 mg/dL) and HbA1c percentage achieved at Week 16 • Correlation of patients reaching 60 units/day insulin glargine U100 and TIR >70% • Change in HbA1c percentage from baseline to Week 16
PRO Objective • To assess patient-perceived treatment impact on health-related quality of life (HRQoL) and treatment satisfaction	**PRO Endpoint** • Change from baseline to Week 16 in diabetes medication treatment satisfaction scores (total score and by subscales), using the Diabetes Medication Satisfaction Tool (DM-SAT) questionnaire
Safety Objective • To assess the safety and tolerability of Soliqua 100/33	**Safety Endpoints** Safety evaluations will include evaluation of the following (for 16 weeks): • Overall hypoglycemia • Confirmed hypoglycemia o ADA Level 1: Measurable glucose concentration

	<70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) ○ ADA Level 2: Measurable glucose concentration <54 mg/dL (3.0 mmol/L) that needs immediate action ○ ADA Level 3: Severe event characterized by altered mental and/or physical functioning that requires assistance* from another person for recovery • AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs)

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

Study Population:

Key Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent, provides signed written informed consent, is willing and able to complete the electronic diary (eDiary), and agrees to comply with protocol requirements (confirmed by the site staff performing the recruitment efforts).
2. Is an adult ≥18 years of age.
3. Has an HbA1c ≥9%-13% during the run-in period.
4. Was diagnosed with T2DM at least 6 months before the baseline period.
5. Has been treated with 2+ OADs with or without GLP-1 RAs with stable doses (for both) for 3 months before the screening period.
6. Is willing and able to wear the CGM device continuously for 14 days to capture CGM measures at baseline (from Visit 2 [ie, the run-in period] until the next site visit at Visit 3.1) and again at the end of the treatment period [ie, from Visit 6 until the next site visit at Visit 7; Section 13.1).
7. Is willing and able to prick fingers a minimum of 2 to 4 times per week, using sterile lancets provided with a manual blood glucose meter kit.

8. Is willing to discontinue daily (oral or injectable) or weekly GLP-1 RA or DPP-4i before administration of Soliqua 100/33.
9. Is willing and able to inject Soliqua 100/33 and increase dose as needed to achieve SMPG target.

Key Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Has T1DM or any other types of diabetes, except T2DM.
2. Is being treated with meglitinides (eg, nateglinide, repaglinide).
3. Has a body mass index (BMI) >40 kg/m² during the screening period.*

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

4. Provides less than equivalent of 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period (eg, days of CGM device wear × % time CGM device active < 8; Section 6.2.1).
5. Has any current or previous skin conditions, including (but not limited to) severe psoriasis, burns, eczema, scarring, and excessive tattoos, that would inhibit the proper wearing of the CGM device.
6. Has a history of severe nausea and vomiting that resulted in subsequent discontinuation of GLP-1 RA.
7. Has a known history or presence of clinically significant pancreatitis or gastroparesis.
8. Has had an episode of severe hypoglycemia or hypoglycemia unawareness (defined as the onset of neuroglycopenia before the appearance of autonomic warning symptoms [for example, blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion] or as the failure to sense a significant fall in blood glucose below normal levels) within the 6 months before the screening period.
9. Has any clinically significant abnormality identified from the physical examination, vital sign measurements, or laboratory tests (eg, amylase, lipase, alanine aminotransferase [ALT] >3 × upper limit of normal [ULN], calcitonin ≥20 pg/mL, severe renal impairment [estimated glomerular filtration rate <30 ml/min/1.73m^2] or end-stage renal disease) or visual

impairment at screening that, in the opinion of the investigator or any qualified designee, would make implementation of the protocol or interpretation of the study results difficult or would preclude safe participation in the study.

10. Has personal or immediate family history of medullary thyroid cancer (MTC) or a genetic condition that predisposes the participant to MTC (eg, multiple endocrine neoplasia syndromes).
11. Has current or known history of alcohol or drug abuse within 6 months before the screening period.
12. Has significant current (within past 2 months) or expected use of medications known to affect glycemia (eg, ≥5 mg/day prednisone).
13. Uses substances known to interfere with CGM readings, such as aspirin-containing products (>650 mg/day of salicylic acid) or supplements containing vitamin C (>1000 mg/day of ascorbic acid) taken during the 14-day periods of CGM measure at baseline (ie, from Visit 2 to Visit 3.1) and end of the treatment period (ie, from Visit 6 to Visit 7).
14. Has undergone previous treatment with any insulin (except for short-term treatment due to intercurrent illness, including gestational diabetes, at the discretion of the investigator).
15. Is enrolled in another clinical study or has taken other investigational drug(s) within 1 month or 5 half-lives from screening, whichever is longer.
16. Has a hypersensitivity to Soliqua 100/33, either of its active components (insulin glargine or lixisenatide), or any of its excipients that, in the opinion of the investigator, contraindicates participation in the study.
17. Has used weight loss drugs (including over-the-counter and herbal medications) within 12 weeks before the screening visit.

Study Design: This is a 16-week, multicenter, interventional, open-label, single-arm, Phase 4 study using blinded CGM (FreeStyle Libre Pro) to demonstrate improvement in the percentage of TIR from baseline in patients adding Soliqua 100/33 and treated for 16 weeks. The study will be conducted in approximately 100 patients whose T2DM is very uncontrolled on 2+ OADs with or without GLP-1 RAs (with stable doses for 3 months), as evident from a screening HbA1c of ≥9%-13%. The study will attempt to represent the diversity of the

US patient population with T2DM **through site recruitment efforts**.

All eligible participants will undergo 14 days of blinded continuous CGM monitoring at baseline (the run-in period) and a mixed-meal tolerance test (MMTT) while on baseline medications. Soliqua 100/33 treatment will be initiated on Day 0 (Visit 3.2), after the MMTT (which is scheduled at Visit 3.1). Sulfonylurea (SU) doses should be down-titrated by 50% when starting Soliqua 100/33, and the last doses of daily dipeptidyl peptidase-4 inhibitor (DPP-4i) and daily GLP-1 RA (oral or injectable) should be administered on the morning of Day –1, the day before the first dose of Soliqua 100/33 (Section 13.1).

At Visit 3.1, participants on OADs or an oral or injectable GLP-1 RA will be required to take their dose after blood sample for fasting plasma glucose (FPG) and HbA1c is collected and 30 minutes before administration of the meal during the MMTT (during which measures for both β-cell function and PPG analyses will be captured). Participants on a weekly GLP-1 RA should have their baseline MMTT conducted within 7 (± 3) days after their last dose and administer their last weekly GLP-1 RA dose 7 (± 2) days before the first dose of Soliqua 100/33.

During the end of the treatment period (from Visit 6 to Visit 7), participants will again be required to undergo 14 days of blinded continuous CGM monitoring and a MMTT (only to derive PPG measures). Soliqua 100/33 should be administered 30 minutes before administration of the meal during the MMTT at Visit 7 (during which only measures for PPG analyses will be captured).

All participants will be allowed to continue their background OADs (except DPP-4i and SU, as previously described) at stable doses and regimens throughout the study period, unless they have to be stopped or modified for safety reasons.

The study comprises the following periods:

- A screening period of up to 2 weeks.
- A run-in period of 2 weeks, including the baseline period.
    - At Visit 2, the CGM device will be applied to the back of the upper arm of the participant and baseline CGM data will be collected continuously for 14 days; the device will be removed at the subsequent site visit during the baseline period (ie, Visit 3.1), after the MMTT.

- During the baseline period, on Day –1 (Visit 3.1), participants will return to the site for the MMTT (for both β-cell function and PPG measures) and CGM removal and data download (after the MMTT). Dispensing of the Soliqua 100/33 pen and instruction on administration of Soliqua 100/33 will also take place during this visit.
- Visit 3.2 (ie, Day 0) during the baseline period is the first day of Soliqua 100/33 administration and includes a phone contact to ALL participants to ensure that all administration procedures were successfully executed and to answer any questions. (Note: The first day of Soliqua 100/33 administration [ie, Visit 3.2, Day 0] for participants on weekly GLP-1 RA will depend on their administration schedule and may not be the day immediately following Visit 3.1. Soliqua 100/33 administration for these participants should be 7 [± 2] days after their last weekly GLP-1 RA dose.)
  - **A phone contact should** also be made **ONLY to participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation**, to remind them of the next morning's injection and to provide instructions for SoloStar pen use. The participants will provide their concomitant medication details to the site personnel over the phone.

- A 16-week, open-label treatment period.
  - Visit 3.2 (ie, Day 0) is the first day of Soliqua 100/33 administration and begins the open-label treatment period (with different initiation requirements based on weekly or daily GLP-1 RA use, as explained above).
  - The dose of Soliqua 100/33 will be adjusted during the titration period (ie, from Weeks 1 through 12; Visits 4.0 to 5.4), at the investigator's discretion, until the desired fasting SMPG value (80-100 mg/dL) is achieved (Table: Recommended Dose Adjustment Algorithm for Soliqua 100/33).
  - During Visits 4.0 to 4.6, weekly phone contacts for dose adjustments are to continue at the investigator's discretion until the desired fasting SMPG value is achieved.
  - If the desired fasting SMPG value is not achieved in the first 8 weeks of treatment, the investigator has the option to continue weekly dose titration phone contacts for an

additional 4 weeks (until Week 12; ie, from Visits 5.1 to 5.4) with the purpose of achieving glycemic targets.

- At Visit 6, a blinded CGM device will again be applied to the back of the upper arm of the participant and CGM data will be collected continuously for 14 days; the device will be removed at the subsequent site visit (ie, Visit 7), after the MMTT (only to derive PPG measures).
- At the end of the study (ie, Visit 7), participants should discuss with the investigator, in collaboration with their HCP, whether to remain on the Soliqua 100/33 treatment regimen or transition to an alternate antihyperglycemic therapy.

- A 2-week post-treatment safety follow-up period after the last dose of Soliqua 100/33 (eg, treatment completion) or after premature/permanent treatment discontinuation from Soliqua 100/33.

Estimated Study Duration:

The total duration of the study will be approximately 22 weeks for each participant. Three site visits, 3 site or home visits, and up to 13 phone contacts are scheduled.

Participants will have the choice to have Visits 2, 5, and 6 performed at the study site or at home. This choice is to be determined at the screening visit. Participants who opt for site visits should be encouraged not to change to home visits during the study period. However, if this is unavoidable, the home health provider and the sponsor-approved courier company for investigational medicinal product (IMP) shipment will need at least 72 hours' notice from the investigator to arrange a home visit and direct-to-patient (DTP) IMP supply, if required. An unscheduled site or home visit can be planned during the treatment period for IMP Soliqua 100/33 resupply, if required. If DTP Soliqua 100/33 supply is required, the sponsor-approved courier company will need at least 72 hours' notice to collect Soliqua 100/33 treatment kits from a study site. The end of the study is defined as the date of the last visit of the last participant in the study. Although Sanofi has every intention of completing the study, Sanofi reserves the right to discontinue the study at any time for clinical or administrative reasons.

Efficacy Assessments:

The schedule of events (SoE) is provided in Section 13.1.

The efficacy assessments are as follows:

- CGM measures.
- MMTT-derived β-cell function and PPG measures.
  - Biomarkers of β-cell function (plasma glucose, insulin, and C-peptide) will be collected at baseline; whereas only plasma glucose will be collected at Visit 7.
- Fasting SMPG.
- FPG measurements.
- HbA1c measurements (during the screening and run-in periods and at Visits 3.1 and 7).

CGM Measures

Blinded CGM will be performed for 14 continuous days during baseline (ie, from Visit 2 to Visit 3.1) and again for 14 days at the end of the treatment period (ie, from Visit 6 to Visit 7; Section 13.1). The baseline CGM measure will be captured before discontinuing the daily (oral or injectable) or weekly GLP-1 RA, DPP-4i, or down-titration of SU by 50%, and before initiation of Soliqua 100/33 treatment. The blinded CGM device (FreeStyle Libre Pro) will be applied to the back of the upper arm of the participant and activated at Visit 2 (ie, the run-in period). Participants will be required to wear the device continuously for 14 days for baseline CGM data collection, with device removal and data download on Day –1 at their next site visit during the baseline period (ie, Visit 3.1), after collection of C-peptide, insulin, and plasma glucose data from the MMTT. Downloaded CGM data will be reviewed by the investigator to determine participants' study eligibility. (Note: During the run-in period, CGM device reinsertion will be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data [not necessarily consecutive] over a 14-day period as a result of premature sensor failure [eg, days of CGM device wear × % time CGM device active < 8]; Table 6-1 and Figure 13–1.) Similarly, participants will be required to continuously wear the device for 14 days at the end of the treatment period from Weeks 14 to 16 (ie, Visit 6 to Visit 7) to collect CGM data, with device removal and data download on the fifteenth day after CGM placement (ie, Visit 7), after collection of only plasma glucose data from the MMTT. Downloaded CGM data will be verified by the investigator at the site to determine participants' study completion. During the end of the treatment period, CGM device reinsertion will also be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not

necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8; Table 6-1 and Figure 13–1), if data can be captured during the 14-day end of treatment window. (Note: The minimum requirement for evaluable CGM data is if at least 10 out of 14 days [not necessarily consecutive] have at least ≥80% of evaluable CGM data per 24-hour period during the run-in period as well as the end of the treatment period [ie, from Weeks 14 to 16]; Battelino et al 2020.)

Participants with less than equivalent of 8 days of evaluable CGM data (not necessarily consecutive) of a 14-day period (eg, days of CGM device wear × % time CGM device active < 8) during the run-in period will be considered as screen failures. For participants who discontinue study treatment prematurely, the visit window can be extended by 14 days to collect the CGM data before they permanently discontinue the treatment.

MMTT-Derived β-Cell Function and PPG Measures

Participants will undergo the MMTT (while wearing the CGM device) to assess maximum PPG exposure in the 4-hour period after the breakfast meal (tested at a central laboratory) with biomarkers of β-cell function (plasma glucose, insulin, and C-peptide) measured at Visit 3.1 (ie, site visit during the baseline period). The baseline MMTT will be conducted before discontinuing the daily (oral or injectable) or weekly GLP-1 RA, DPP-4i, or down-titration of SU by 50%. Participants on OADs or an oral or injectable GLP-1 RA will be required to take their dose after the blood sample for FPG and HbA1c is collected and 30 minutes before administration of the meal during the MMTT (Visit 3.1). Participants who are on weekly GLP-1 RA should have their baseline MMTT conducted within 7 (± 3) days after their last dose. During baseline (Visit 3.1), blood samples will be collected at the following time points: premeal (30 min) and just before administration of OADs or GLP-1 RA (oral or injectable) (baseline); time 0 (just before the meal), 10 min, 20 min; and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 hours post-meal for plasma glucose, C-peptide, and insulin levels.

At the end of the treatment period (Visit 7), participants will again undergo the MMTT (while wearing the CGM device; only to derive PPG measures). Soliqua 100/33 should be administered 30 minutes before administration of the meal during the MMTT at Visit 7. At the end of the treatment period (Visit 7), blood samples will be collected for plasma glucose levels, as follows: premeal (30 min) and just before administration of Soliqua 100/33; and time 0 (just

before the meal), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 hours post-meal. These values will be used for PPG analyses with the goal of deriving reduction in the maximum glucose exposure in the 4-hour period after the breakfast meal following Soliqua 100/33 administration for 16 weeks compared with baseline. During both baseline and end-of-treatment assessments, removal of the CGM device and download of data will be done after completion of the MMTT (Section 13.1).

The MMTT includes a standardized meal (ie, Boost Very High Calorie) that contains approximately 530 kcal and is composed of 19% carbohydrates, 44% protein, and 33% fat. The composition and the quantity of the standardized meal must be identical throughout the study period.

During the baseline period (ie, Visit 3.1), on the day of the MMTT, the participants 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). At the end of the treatment period (ie, Visit 7), the MMTT will also be performed in a fasted state (eg, no consumption of any food or drink for at least 8 hours, except water, before the scheduled meal test), and participants will receive their Soliqua 100/33 dose at the site 30 minutes before the start of the test (ie, consumption of the meal and just after the first blood draw).

For participants who discontinue study treatment prematurely, the visit window can be extended by 14 days to collect the CGM data, followed by the MMTT data, before they permanently discontinue the treatment.

Fasting SMPG

Participants will be supplied with a glucometer and an eDiary at the screening visit. Appropriate training will be provided to the participants related to proper use of the glucometer and eDiary completion. Fasting SMPG values (lowest values in conjunction with measurements from the previous 3 days) will be used to titrate and adjust Soliqua 100/33 doses and monitor glycemic control. The participants are required to measure fasting SMPG values before breakfast at least 3 to 4 times per week throughout the study period (to inform each dose adjustment) and record the results in the eDiary. During the titration period, fasting SMPG should be performed on each of the 3 to 4 days before each dose adjustment. (Note: Additional titration is at the discretion of the investigator with the goal of achieving glycemic targets while minimizing the risk of hypoglycemia and hyperglycemia.)

SMPG During Symptomatic Hypoglycemia

Whenever participants experience hypoglycemia symptoms, they (or others, if applicable) should measure plasma glucose, if possible. Participants should be instructed to measure plasma glucose levels before carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate carbohydrate/glucose rescue before confirmation with the SMPG values. Participants must contact the investigator as soon as possible following hypoglycemia events for review and so that a decision regarding any necessary actions can be made. Participants should be instructed to measure plasma glucose levels again after the event resolves.

FPG Measurements

Blood samples will be collected to determine FPG at the time points specified in the SoE (Section 13.1) and will be measured at a central laboratory. For the scheduled site visits, participants are required to arrive fasting without administering the Soliqua 100/33 injection. Fasting is defined as no food intake in the 8 hours before blood sampling, except water.

HbA1c Measurements

Blood samples will be collected to measure HbA1c during the screening and run-in periods, and at Visit 3.1 (before administration of the meal) at the central laboratory, to determine study eligibility, and at the end of the 16-week treatment period (Visit 7), to determine change in glycemic control.

Assessment of PRO

Diabetes Medication Satisfaction Tool

The assessment of treatment-related impact on participants' health-related quality of life and their satisfaction with diabetes therapy will be assessed using the DM-SAT questionnaire (Anderson et al 2009) at the baseline visit before stopping or down-titration of baseline therapies and at the end of the treatment period (Section 13.1). The DM-SAT questionnaire (Section 13.2) is a 16-item measure with 4 subscales assessing wellbeing (3 items), medical control (3 items), lifestyle (5 items), and convenience (5 items).

Participants will be requested to complete the DM-SAT questionnaire by themselves, independently from the investigator or site staff, and without any help from friends or relatives. For validity purposes, the questionnaire should be completed by participants in a

quiet place, at the start of the visit before any other study tests or procedures are performed or Soliqua 100/33 is administered.

Safety Assessments:

Safety will be evaluated by the frequency, severity, seriousness, and duration of any AEs. Hypoglycemia events, AEs, and SAEs, including AESIs, will be recorded at each site visit and phone contact throughout the study period.

Any abnormal changes in vital signs, standard chemistry, and hematology will be assessed at Visit 1 (ie, screening period), Visit 3.1 (ie, before initiation of Soliqua 100/33 treatment), and Visit 7 (ie, end of the treatment period; Section 13.1).

The safety assessments are as follows:

- Physical examination.
- Hypoglycemia events.
- AEs and SAEs, including AESIs.
- Vital signs (heart rate, systolic blood pressure [BP], and diastolic BP).
- Clinical safety laboratory assessments (eg, clinical chemistry, calcitonin [screening only], hematology, urinalysis).

Physical Examination

A complete physical examination (including body weight) will be performed, per standard of care, in order to assess the health status of the participants at time points described in the SoE (Section 13.1). Height measurements in conjunction with body weight will be utilized to calculate BMI during the screening period.

Hypoglycemia Events

During the study, participants must be instructed to document any hypoglycemia events in their eDiary. Hypoglycemia will be reported in the specific hypoglycemia event information form in electronic case report form (eCRF) with onset date and time; symptoms and/or signs; the SMPG value, if available; and the treatment. A hypoglycemia event that fulfills the seriousness criteria will also be documented on the SAE form in the eCRF. Participants should be instructed to record their SMPG values in the eDiary after the event resolves.

Hypoglycemia will be evaluated in accordance with the consensus report of a steering committee on levels of hypoglycemia (Agiostratidou et al 2017). These levels are consistent with the ADA standard of care 2021 recommendations (ADA 2021a).

The following are the categories of interest:

- Overall hypoglycemia.
- Confirmed hypoglycemia.
  - ADA Level 1: A measurable glucose concentration of <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L).
  - ADA Level 2: A measurable glucose concentration of <54 mg/dL (3.0 mmol/L) that needs immediate action.
  - ADA Level 3: A severe event characterized by altered mental and/or physical functioning that requires assistance* from another person for recovery.

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

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

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

All AEs (serious or nonserious) will be collected from the signing of the informed consent form (ICF) until the follow-up visit (Section 13.1). The definitions of AEs and SAEs are provided in the Section 13.5.

AESI: An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

The following AEs will be considered AESIs in this study:

- Pregnancy of a female participant enrolled in the study as well as pregnancy occurring in a female partner of a male participant enrolled in the study with IMP/non-investigational medicinal product (NIMP).
- Symptomatic overdose (serious or nonserious) with IMP/NIMP.

- An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the investigator or spontaneously reported by the participant and is defined as any dose administration that, in the investigator's opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin or is at least twice the intended dose within the intended therapeutic interval (for example, for a participant prescribed 60 units/20 µg Soliqua 100/33 once a day, administration of ≥120 units of insulin glargine U100 with ≥40 µg of lixisenatide once a day would be considered an overdose), adjusted according to the tested drug.

- Increase in ALT (>3 × ULN; Section 13.6).

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. The investigator remains responsible for following up on AEs that are serious, considered related to the study treatment or study procedures, or caused the participant to discontinue the Soliqua 100/33 treatment and/or the study.

Vital Signs

Vital signs will be recorded at the time points specified in the SoE (Section 13.1).

Clinical Safety Laboratory Assessments

All clinical safety laboratory assessments will be performed by a central laboratory. The investigator must review the laboratory report and document this review. The laboratory reports must be filed with the source documents.

Clinically significant abnormal laboratory findings associated with the underlying disease or vital signs will **not** be considered clinically significant or be reported as AEs **unless** one of the following criteria is met:

- Participant is symptomatic (and/or laboratory values or vital signs are clinically significant per the investigator's discretion).
- Participant requires either corrective treatment or consultation.
- Participant requires Soliqua 100/33 treatment to be discontinued or modification of dosing.
- Event fulfills a seriousness criterion.
- Event meets the definition of an AESI (Section 6.3.5.2).

Pregnancy

A urine pregnancy test will be performed at time points specified in the SoE (Section 13.1). Any female participant who becomes pregnant while participating in the study will be discontinued from study drug treatment.

Study Visits

The SoE is provided in Section 13.1.

- The screening period (Visit 1) will encompass up to 2 weeks and includes obtaining informed consent, eligibility criteria, demographic assessment, review of medical/surgical history and current medications, physical examination (BMI calculation), dispensing of glucometer, HbA1c measurement, setting up the eDiary, recording of vital signs, and clinical chemistry, calcitonin, hematology, urinalysis, and pregnancy tests.
- The run-in period (Visit 2) will encompass 2 weeks, including the baseline period, and includes HbA1c measurement and application of blinded CGM device (FreeStyle Libre Pro).
  - Visit 3.1 will be a site visit and includes assessment of eligibility criteria, MMTT, CGM device removal and data download (after the MMTT), CGM compliance assessment, evaluation of PPG and biomarkers of β-cell function (insulin, C-peptide, plasma glucose) during the MMTT, instructions for certain therapies (eg, DPP-4i, oral daily or weekly GLP-1 RA, and down-titration of SU by 50% when starting Soliqua 100/33), dispensing of Soliqua 100/33 and providing instruction for SoloStar™ pen use, HbA1c and FPG measurements, administration of the DM-SAT, recording of vital signs and body weight, and clinical chemistry, hematology, urinalysis, and pregnancy tests.
  - Visit 3.2 (ie, Day 0) during the baseline period is the first day of Soliqua 100/33 administration and includes a phone contact to ALL participants to ensure that all administration procedures were successfully executed and to answer any questions. (Note: The first day of Soliqua administration [ie, Visit 3.2, Day 0] for participants on weekly GLP-1 RA will depend on their administration schedule and may not be the day immediately following Visit 3.1. Soliqua 100/33 administration for these participants should be 7 [± 2] days after their last weekly GLP-1 RA dose.)
    - **A phone contact should** also be made **ONLY to participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation,** to remind them of the next

morning's injection and to provide instructions for SoloStar pen use. The participants will provide their concomitant medication details to the site personnel over the phone.

- The treatment period will encompass up to 16 weeks (Visits 3.2 through 7), and includes the following:
  - Visit 3.2 (ie, Day 0) is the first day of Soliqua 100/33 administration and begins the open-label treatment period (with different initiation requirements based on weekly or daily GLP-1 RA use, as explained above).
  - Titration period (Visits 4.0 to 4.6, 5, and 5.1 to 5.4).
    - For Visits 4.0 to 4.6, titration of the Soliqua 100/33 dose will occur via phone contacts, but it can occur at the study site or at home for Visit 5. For Visits 5.1 through 5.4, titration of Soliqua 100/33 dose will again occur via phone contacts.
    - During the titration period, participants will continue to make entries into their eDiary, administer Soliqua 100/33, adjust the Soliqua 100/33 dose, and capture any product complaints.
    - Other than an unscheduled visit, dispensing of Soliqua 100/33 will occur at Visit 5, if required. A pregnancy test will also be conducted at Visit 5.
  - Visit 6: Application of blinded CGM device, assessment of Soliqua 100/33 adherence, and capturing of any product complaints.
  - Visit 7 (ie, end of the treatment period): Physical examination (including body weight), MMTT (only to derive PPG measures), removal of CGM device and download of data, assessment of Soliqua 100/33 adherence, HbA1c and FPG measurements, recording of the DM-SAT, vital signs, and clinical chemistry, hematology, urinalysis, and pregnancy tests.
  - At the end of the study (ie, Visit 7), participants should discuss with the investigator, in collaboration with their HCP, whether to remain on the Soliqua 100/33 treatment regimen or transition to an alternate antihyperglycemic therapy.
- An unscheduled visit can be performed at any time during the treatment period and may include dispensing of Soliqua 100/33,

adjustment of Soliqua 100/33 dose, review of concomitant medications, and recording of hypoglycemia events and AEs/SAEs (including AESIs).

- The follow-up safety period (Visit 8) will occur 2 weeks after the end of the treatment period.
- Fasting SMPG values and those measures required to manage hypoglycemia events will occur from the run-in period (Visit 2) through the end of the treatment period (Visit 7).
- Soliqua 100/33 dosing will occur from the end of the baseline period (Visit 3.2) through the end of the treatment period (Visit 7).
- eDiary completion, recording of hypoglycemia events, and AEs/SAEs (including AESIs) will occur from the screening period (Visit 1) through the follow-up period (Visit 8), whereas review of concomitant medications will occur from the baseline period (Visit 3.1) through the follow-up period (Visit 8).

Study Drug, Dosage, and Route of Administration:

- Formulation: Soliqua 100/33 will be supplied as a sterile, non-pyrogenic, clear, colorless solution in SoloStar prefilled (disposable) pen for subcutaneous (SC) injection. The SoloStar pen is necessary for Soliqua 100/33 administration, and it is considered an integral part of the Soliqua 100/33 therapy.
  - The prefilled SoloStar disposable pen contains 3 mL of sterile solution containing 100 units/mL insulin glargine and 33 µg/mL lixisenatide in a 3:1 ratio (ie, 3 units of insulin glargine to 1 µg lixisenatide), and it allows for administration of both ingredients simultaneously with doses ranging from 15 units/5 µg to 60 units/20 µg (insulin glargine U100/lixisenatide).
  - Soliqua pen instructions will be given to all participants at Visit 3.1.
  - A phone contact should be made to **participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation,** to remind them of the next morning's injection and to provide instructions for SoloStar pen use.
- Route of administration: SC injection using the SoloStar pen into the abdominal area, thigh, or upper arm. Injection sites should be rotated within the same region from one injection to the next to reduce the risk of lipodystrophy.

- Time of administration: Soliqua 100/33 should be self-administered once-daily in the morning approximately 60 minutes before breakfast.
    - The first dose of Soliqua 100/33 will be administered on the morning of Day 0 (ie, Visit 3.2). This date should be 7 [± 2] days after the last weekly GLP-1 RA dose or the morning following the last dose of DPP-4i, or daily GLP-1 RA (oral or injectable) administration.

Starting Dose

- For all participants, the starting dose of Soliqua 100/33 will be 15 units of insulin glargine (corresponding to 5 μg of lixisenatide).
- The maximum daily dose of Soliqua 100/33 should not exceed 60 units of insulin glargine (corresponding to 20 μg of lixisenatide).

Dose Modifications

The dose of Soliqua 100/33 will be adjusted with the aim of attaining a target fasting SMPG value of 80 to 100 mg/dL. The dose will be adjusted based on the lowest fasting SMPG values in conjunction with measurements from the previous 3 days throughout the study period. During the titration period (ie, Weeks 1 through 12) fasting SMPG should be assessed on each of the 3 to 4 days before each dose adjustment. During the titration period, the dose of Soliqua 100/33 should be adjusted upwards or downwards by 2 to 4 units every week (with additional titration also at the discretion of the investigator in accordance with the participant's blood glucose monitoring results) with the goal of achieving a fasting SMPG value of 80 to 100 mg/dL, as well as other glycemic goals, while minimizing the risk of hypoglycemia and hyperglycemia. The duration of the titration period and number of phone contacts to safely meet the study goals will also be at the discretion of the investigator.

As stated above, dose titration is at the discretion of the investigator. Study participants should be trained and retrained on an ongoing basis to establish proper understanding of titration procedures because very close communication between the participant and the study site is necessary to ensure adequate titration while minimizing the associated risks. Investigators may adjust or stop titration or temporarily reduce the dose if they believe further titration would result in participants experiencing any AEs (eg, hypoglycemia, AESIs). After the target fasting SMPG value has been achieved, the

dose of Soliqua 100/33 will be adjusted as necessary until the end of the study to maintain the target fasting SMPG value in accordance with the dose titration guidelines provided in the following table. If the desired fasting SMPG target is not achieved in the first 8 weeks of treatment, the investigator has the option to continue weekly dose titration phone contacts for an additional 4 weeks (until Week 12) for the purpose of achieving glycemic targets.

Doses will be adjusted at least weekly, but additional titration may be considered at the investigator's discretion. Participants are, therefore, required to record their fasting SMPG values before breakfast at least 3 to 4 times per week throughout the study period to inform each dose adjustment.

Recommended Dose Adjustment Algorithm for Soliqua 100/33

Median of Fasting SMPG Values (With Lowest Value Considered in Conjunction With Previous 3 Measurements)	**Soliqua 100/33 Dosage Adjustment (Units/Week)**
>140 mg/dL (>7.8 mmol/L)	+4 units
>100 to ≤140 mg/dL (>5.5 to ≤7.8 mmol/L)	+2 units
Glycemic target: 80 to 100 mg/dL (4.4–5.5 mmol/L), inclusive	No change
≥60 to <80 mg/dL (≥3.3 to <4.4 mmol/L)	–2 units
<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemia events or 1 severe hypoglycemia event (requiring assistance) documented in the preceding week	–2 to –4 units or at the discretion of the investigator or any qualified designee

Notes: Dose changes should also be based on the median SMPG values (with the lowest value considered in conjunction with the previous 3 measurements). If the lowest value from the previous 3 measurements is from 80 to 100 mg/dL and the other 2 values are well above 100 mg/dL, further titration may be implemented at the investigator's discretion. If the lowest value is <70 mg/dL and the other 2 values are near 100 mg/dL, the investigator may stop or temporarily reduce the dose if, in their judgment, further titration would be hazardous.

NIMP and Concomitant Therapy

Background OADs (eg, SU, biguanides, thiazolidinediones, α-glucosidase inhibitors, sodium-glucose co-transporter-2 [SGLT2] inhibitors, bile acid sequestrants, dopamine agonists) are permitted during the screening and treatment periods of the study, initiated and at stable doses for a minimum of 3 months before the screening period. Meglitinides will be prohibited (eg, repaglinide, nateglinide).

Appropriate Corrective Action/Rescue Therapy

Titration will be exceedingly important throughout the first 12 weeks of this study and will require consistent reviews of fasting SMPG values, the daily insulin dose, and hypoglycemia events to identify participants whose Soliqua 100/33 dose is not being appropriately managed.

If after Week 12 (ie, end of the titration period), the participant's FPG level is >240 mg/dL with no reasonable explanation for severe hyperglycemia, such as intercurrent illnesses or nonadherence to instructed titration, the investigator should obtain an HbA1c measurement and decide whether rescue therapy is warranted.

Devices

Blood Glucose Meter Kit: Each study participant will be provided with a blood glucose meter kit, in order to perform SMPG assessments. The blood glucose meter kit will include a blood glucose meter, lancing device, test strips, sterile lancets, storage box, control solution, and instructions for use.

CGM Device (FreeStyle Libre Pro Flash Glucose Monitoring System): The device will be applied to the back of the upper arm of each participant, and they will be required to wear it continuously for 14 days during CGM data collection both at baseline (during the run-in period) and for 2 weeks at the end of the treatment period (ie, Weeks 14 to 16).

Management of Clinical Supplies

Study Drug Packaging and Storage

Packaging will be 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 (including pen needles as ancillary supplies) will be dispensed to provide participants with Soliqua 100/33 coverage up to the next site visit or phone contact with DTP Soliqua 100/33 delivery (Section 13.1). Storage conditions and use-by-end date (ie, expiry date) are part of the Soliqua 100/33 label text.

Investigators or other authorized persons (eg, pharmacists, IMP managers) are responsible for storing Soliqua 100/33 in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures. Control of Soliqua 100/33 storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling the Soliqua 100/33 should be managed according to the rules provided by the sponsor.

Study Drug Accountability

The investigator or other personnel designated by the investigator will maintain accurate records of receipt of study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each participant in the study. The investigator or other personnel designated by the investigator will also be responsible for controlling the site stocks of Soliqua 100/33 and requesting any resupply, as needed.

All Soliqua 100/33 will be dispensed in accordance with the investigator's oversight. It is also the investigator's responsibility to ensure that an accurate recording of Soliqua 100/33 kits issued and returned is maintained.

Any quality issue noticed with the receipt or use of Soliqua 100/33 pen (deficiency in condition, appearance, documentation, labeling, expiration date, etc.) must be promptly reported to the sponsor.

Under no circumstances will the investigator supply Soliqua 100/33 pens to a third party (except for DTP shipment, for which a courier company has been approved by the sponsor), allow the Soliqua 100/33 pen to be used other than as directed by this clinical study protocol, or dispose of the Soliqua 100/33 pen.

Overdose Management

An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the investigator or spontaneously reported by the participant and is defined as any dose administration that, in the investigator's opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin or is at least twice the intended dose within the intended therapeutic interval. Any overdose, with or without associated AEs, must be promptly reported in eCRFs by the sites, which will then be notified to the sponsor's representative (ie, PPD Pharmacovigilance). Overdoses without signs or symptoms should be recorded as a standard overdose; any AEs associated with the overdose should be reported on the relevant AE/SAE sections in the eCRF.

Treatment of Overdose

Insulin Glargine

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in study drug dose, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

Lixisenatide

During clinical studies, doses up to 30 µg of lixisenatide twice daily (3 times the daily recommended dose) were administered to patients with T2DM in a 13-week study. Increased incidence of GI disorders was observed (Soliqua 2019).

In case of overdose, appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms, and the Soliqua 100/33 dose should be reduced to the prescribed dose.

Treatment Adherence

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

The monitor in charge of the study will check the data entered on the Soliqua 100/33 administration page of the eCRF by comparing them with the Soliqua 100/33 study drug that has been returned and the participant's treatment log form.

Sample Size:

Sufficient participants will be screened from approximately 15 sites to include 100 patients, such that approximately 82 evaluable participants complete the study (anticipating that approximately 15% of participants discontinue the study before Week 16).

Determination of Sample Size

The sample size is based on the primary objective to demonstrate the significant mean change (ie, increase) in the percentage of TIR (70-180 mg/dL) from baseline to Week 16 with sufficient power. A

sample size of 82 patients will have 95% power to detect an absolute increase in TIR means of 10%, assuming a standard deviation (SD) of 25 for the change in TIR, with a two-sided type I error of 0.05. Anticipating a 15% loss to follow-up rate, 100 patients would need to be enrolled.

Statistical Methods:

Analysis Sets

- Enrolled set: All eligible participants who are dispensed Soliqua 100/33 and sign the ICF.
- Efficacy analysis set: All enrolled participants who receive ≥1 dose of Soliqua 100/33 and have evaluable CGM data at baseline.
- Safety set: All enrolled participants who receive ≥1 dose of Soliqua 100/33.

General Statistical Methods

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 participants having non-missing assessments at a specific visit). The baseline value is defined as the last available value before the first injection of Soliqua 100/33.

All efficacy analyses (primary, key secondary, secondary, and other efficacy endpoints) will be performed on the efficacy analysis set.

Analysis of demographics, baseline characteristics, and prior and concomitant medications will be provided in detail in the statistical analysis plan (SAP).

The extent of study treatment exposure and adherence will be assessed and summarized with dose frequency and duration of treatment.

Continuous data will be summarized using number of observations available, mean, SD, quartile ranges, minimum, median, and maximum. Categorical data will be summarized using count and percentage.

Primary Analysis

Mean change in the percentage of TIR (70-180 mg/dL) from baseline to Week 16 and its associated 95% confidence interval (CI). A one-sample t-test will be applied to test the significance of changes at Week 16 over baseline. A p-value <0.05 will be considered significant.

Key Secondary Analysis

Mean changes for continuous outcomes (eg, CV, mean daily blood glucose, maximum PPG exposure in the 4 hours after the breakfast meal, TAR >180 mg/dL) will be presented at baseline and at the end of the treatment period (Week 16). Mean (SD) and associated 95% CI, as well as minimum, median, and maximum will be provided.

Analysis of Secondary Endpoints

- Mean changes for continuous outcomes will be presented at baseline and at the end of the treatment period (Week 16). Mean (SD) and associated 95% CI, as well as minimum, median, and maximum will be provided.
- Binary outcomes will be summarized with proportions and 95% CI using the Clopper Pearson exact method.

Analysis of Other Efficacy Endpoints

- Mean changes for continuous outcomes will be presented at baseline and at the end of the treatment period (Week 16). Mean (SD) and associated 95% CI, as well as minimum, median, and maximum will be provided.
- The correlation of TIR to PRO, HbA1c, and requirement for 60 units/day of insulin glargine U100 (related to TIR >70%) at Week 16 will be assessed using Pearson correlation coefficient.

Analysis of PRO Endpoint

- Change in diabetes medication treatment-related impact and satisfaction, as measured by the DM-SAT, from baseline to Week 16 will be analyzed using the efficacy analysis set and described as mean (SD) and associated 95% CI as well as minimum, median, and maximum for overall score and by subscales.

Safety Endpoints

All safety and tolerability endpoints will be described by number, proportions, and the associated 95% CI for proportions. Adverse event incidence tables will be presented by system organ class (SOC; sorted by internationally agreed order), high-level group term (HLGT), high-level term (HLT), and preferred term (PT) sorted in alphabetical order with the number (n) and percentage of participants experiencing an AE. Participants with more than 1 AE episode will be counted only once. The denominator for computation of percentages will be the safety set. Hypoglycemia events will be counted with multiple episodes per participant, if

available, and the event rate per person-years will be reported overall and by level.

Handling of Missing Data

Missing data will be handled differently in accordance with the reasons for the missing data for both primary and key secondary endpoints. If the missing data are due to technical issues with the CGM device (ie, CGM data are not evaluable if at least 10 out of 14 days [not necessarily consecutive] have <80% of evaluable CGM data per 24-hour period during the run-in period as well as the end of the treatment period [ie, from Weeks 14 to 16]), the participant will be excluded from the analysis (missing completely at random [MCAR] approach). For other reasons for missing measurements (eg, lost to follow-up, discontinued treatment), the baseline value carried forward (MCAR, conservative approach) is planned for both primary and key secondary analyses.

Multiple Comparisons and Multiplicity

A hierarchical testing procedure will be performed. Key secondary endpoints will be evaluated with a one-sample t-test to determine whether there is any change at Week 16 over baseline in succession in accordance with the hierarchy and as long as the endpoints continue to show statistical significance. If one test is nonsignificant ($p > 0.05$), then the testing will be stopped (or consider all further tests to be only secondary, and no formal conclusions can be drawn).

Study Committees: Scientific steering committee: No

Adjudication committee: No

Data monitoring committee: No

Date of Protocol: 18 Aug 2021

List of Abbreviations

Abbreviation	Definition
ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-4h}	area under the concentration versus time curve from time 0 to 4 hours
BMI	body mass index
BOCF	baseline observation carry forward
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CGM	continuous glucose monitoring
CNIL	Commission Nationale de l'Informatique et des Libertés
CONSORT	Consolidated Standards of Reporting Trials
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DM-SAT	Diabetes Medication Satisfaction Tool
DPP-4i	dipeptidyl peptidase-4 inhibitor
DTP	direct-to-patient
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data collection
eDiary	electronic diary
EU	European Union
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice

Abbreviation	Definition
GDPR	General Data Protection Regulation
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide 1 receptor agonist
GMI	Glucose Management Indicator
HbA1c	glycated hemoglobin
HCP	healthcare provider
HLGT	high-level group term
HLT	high-level term
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IR	Investigator Registry
IRB	institutional review board
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
LLOQ	lower limit of quantification
LS	least square
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	mixed-meal tolerance test
MNAR	missing not at random
MODD	mean of daily difference
MTC	medullary thyroid cancer
NIMP	non-investigational medicinal product
OAD	oral antidiabetic drug
OC	observed cases
OTC	over-the-counter
PPG	postprandial glucose

Abbreviation	Definition
PRO	patient-reported outcome
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGLT2	sodium-glucose co-transporter-2
SIP	Shared Investigator Platform
SMPG	self-measured plasma glucose
SOC	system organ class
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to reach maximum concentration
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAR	time above range
TBR	time below range
TIR	time in range
ULN	upper limit of normal
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential

1. Introduction

1.1 Background Information

Diabetes represents a major health burden in the US and had a prevalence of 34.2 million people of all ages in 2018, which is expected to increase to 54 million by 2030. Despite notable advancements in drug discovery, 50% of patients still have a glycated hemoglobin (HbA1c) >7%, and 14% of patients have an HbA1c >9%, signifying poor glycemic control (Centers for Disease Control and Prevention [CDC 2020]; HEDIS Comprehensive Diabetes Care 2021). The 2021 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus report recommends combination therapy with a basal insulin and a glucagon-like peptide-1 receptor agonist (GLP-1 RA) as one approach to glycemic control in patients with type 2 diabetes (T2DM) with HbA1c levels more than 1.5% above their target (Davies et al 2018; ADA 2021b).

In 2017, the total US cost of diagnosed diabetes care was projected to be $237.3 billion (ADA 2018). Approximately 38% of these costs were attributed to hospital-related fees (eg, outpatient treatment [$12.1 billion], inpatient care [$69.7 billion], emergency department costs [$8.0 billion], and ambulance charges [$332.0 million]). Indirect costs associated with loss of productivity and these direct costs account for 73.1% of the total cost of diabetes (Anderson et al 2020). Patients with T2DM, who account for 90% of all US diabetes cases, are often hospitalized or treated in the emergency department for severe hyperglycemia or hypoglycemia. In particular, those patients with fluctuations of HbA1c and very low or very high mean HbA1c levels contribute significantly to these costs (Conn et al 2015; Cannon et al 2018; Critchley et al 2019).

Traditional methods of measuring blood glucose have resulted in substandard glycemic control in many patients with T2DM (Stone et al 2013; Carls et al 2017). Measuring HbA1c provides a retrospective 3-month glucose average with little, if any, information on hypo- or hyperglycemia, which can subsequently lead to microvascular or macrovascular complications. Although self-measured plasma glucose (SMPG), when used within a structured testing program, has demonstrated improved glycemic control and quality of life in people with diabetes (both insulin-treated and noninsulin-treated), it cannot predict impending hyperglycemia, hypoglycemia, or alert for hypoglycemia, and therefore, alternative glucose measurement methods must be considered (Danne et al 2017).

Continuous glucose monitoring (CGM) can address many of the limitations of HbA1c testing and SMPG monitoring, and has contributed to rapid growth amongst specialists and patients in the US over the past few years. Randomized, controlled, clinical studies evaluating CGM use in insulin-requiring individuals have demonstrated improvements in HbA1c, glycemic variability, and increased time in target glycemic range as well as reductions in hypoglycemia events (Anderson et al 2020). Based on the benefits and utility of CGM, several national and international medical organizations have recommended CGM use for people with diabetes who require insulin therapy in type 1 diabetes mellitus (T1DM) and T2DM and/or those at risk for hypoglycemia. Glucose measures captured via CGM are also being considered as a required accompanying measure to HbA1c in clinical studies investigating new diabetes therapies for review and approval by the US Food and Drug Administration (FDA). However, utilization of CGM monitoring in primary care settings has remained low, in part, due to the new skills required to meaningfully and appropriately use the data collected. As the pandemic has propelled primary care into the virtual healthcare arena, the pandemic has also increased patient demand for CGM use. Primary care physicians have developed the skills required to improve telemedicine visits. Similarly, primary care will be forced to embrace the utility of continuously collected glucose data to improve the glycemic management and refine the self-care behaviors of their patients (Johnson and Kayne 2020).

1.2 Rationale

Soliqua™ 100/33 is a fixed-ratio combination of insulin glargine U100 (100 units/mL) plus lixisenatide (33 µg/mL), a GLP-1 RA (Soliqua 2019). The combination of a basal insulin and a GLP-1 RA addresses both fasting and postprandial hyperglycemia, thus ensuring more comprehensive glycemic control than basal insulin alone. The efficacy and safety of Soliqua 100/33 has been clearly established in randomized controlled clinical studies. In the LixiLan-O study, the HbA1c of patients uncontrolled on oral antidiabetic drugs (OADs) who were treated with Soliqua 100/33 decreased from 8.1% (baseline) to 6.5% (end of study) with the majority (74%) achieving the HbA1c target of <7% (Rosenstock et al 2016). The efficacy of Soliqua 100/33 was also demonstrated by a 2.9% HbA1c reduction from baseline, with 74% of patients achieving an HbA1c of <7%, in a subgroup of patients with T2DM with baseline HbA1c ≥9% uncontrolled on OADs from the LixiLan-O study (Davies et al 2019). Similarly, patients uncontrolled on basal insulin in the LixiLan-L study demonstrated an HbA1c reduction from 8.1% to 6.9%, and most (55%) reached their target HbA1c of <7% (Aroda et al 2016). These results were achieved without weight gain and with fewer

gastrointestinal (GI) side effects than with lixisenatide alone, likely due to a more gradual titration of the GLP-1 RA dose (Rosenstock et al 2016; Davies et al 2019).

Continuous glucose monitoring provides a more complete picture of glycemic exposure and excursions than self-monitored blood glucose or HbA1c (Danne et al 2017). In the US, use of CGM is becoming mainstream, driven by improved sensor accuracy, convenience, ease of use, cost-effectiveness, and increased reimbursement. Continuous glucose monitoring facilitates improved glycemic control while reducing hypoglycemia risk (Danne et al 2017; Battelino et al 2019) and is rapidly becoming standard of practice for many healthcare providers (HCPs) for management of patients with T1DM and insulin-treated T2DM.

Time in range (TIR) is one of the metrics derived from CGM and is increasingly utilized to assess glycemic control. It can correlate with HbA1c values as well as the risk of diabetes-related complications (both microvascular and macrovascular). The International Consensus Report on "clinical targets for CGM interpretation" has identified "TIR" as a metric providing more actionable information than HbA1c and has defined targets for clinical use (Battelino et al 2019). For example, in patients with uncomplicated T2DM whose HbA1c targets are <7%, the recommended TIR (for a target range of 70-180 mg/dL) is >70% of the readings.

Soliqua 100/33 is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (Soliqua 2019). The 2021 Standards of Medical Care in Diabetes from the ADA (ADA 2021a; ADA 2021b) recommends the use of fixed-ratio combinations when the combination of individual components is indicated, such as when a GLP-1 RA is added to basal insulin or vice versa. The ADA 2021 Standards also recommend dual combination therapy in individuals with HbA1c values ≥1.5% from their glycemic target (ADA 2021b). Correlations of HbA1c and TIR indicate that CGM glucose readings of patients with an HbA1c ≥9% are in range 40% of the time or less, compared with the 70% TIR associated with an HbA1c of 7% (Battelino et al 2019). Although there are currently no studies using CGM measurements to capture glycemic excursions and variability related to Soliqua 100/33, a post hoc analysis demonstrated improvement in all measures of glycemic variability compared with its individual components (eg, lixisenatide or insulin glargine U100), assessed by 7-point blood glucose profiles. These findings were attributable to Soliqua 100/33's complementary mechanisms of action, which demonstrate reductions in both fasting and postprandial hyperglycemia (Aronson et al 2019).

The current study is intended to replicate these results using CGM to measure TIR and glycemic variability in a patient population with very uncontrolled T2DM (HbA1c ≥9%-13%), who are most likely to benefit from a fixed-ratio combination approach, such as Soliqua 100/33.

The primary objective of this study is to demonstrate an improvement in the percentage of TIR from baseline to the end of the study (16 weeks) in insulin-naïve patients with very uncontrolled (HbA1c ≥9%-13%) T2DM on 2+ OADs with or without GLP-1 RAs.

1.3 Benefit-Risk Assessment

Soliqua 100/33 has demonstrated superior glycemic efficacy in patients with T2DM uncontrolled on oral therapies, basal insulin, or GLP-1 RA (including weekly GLP-1 RA) with durable efficacy (52 weeks) compared with its individual components (insulin glargine U100 and lixisenatide), and recently premixed insulin analog (BIAsp 30) in those uncontrolled on basal insulin and oral therapies (Rosenstock et al 2021). Additionally, compared with insulin glargine U100 alone, patients on Soliqua 100/33 had weight neutrality with no increase in hypoglycemia events; compared with lixisenatide alone, they experienced fewer GI adverse events (AEs) (Aroda et al 2016; Rosenstock et al 2016; Blonde et al 2019). Soliqua 100/33 has also shown greater HbA1c reduction, less weight gain, and less hypoglycemia compared to a premixed insulin analog (BiAsp 70/30) in individuals not controlled on basal insulin therapy (Rosenstock et al 2021). No new risks have been identified for the population to be included in Study LPS16990. In this study, treatment with Soliqua 100/33 will be consistent with the current US FDA-approved label indications (Soliqua 2019). During the titration period, the dose of Soliqua 100/33 will be adjusted upwards or downwards by 2 to 4 units every week, or at the investigator's discretion, based on the participant's blood glucose monitoring results, with the objective of safely attaining a fasting SMPG value of 80 to 100 mg/dL, as well as other glycemic goals, while minimizing the risk of hypoglycemia and hyperglycemia. The duration of the titration period and number of phone contacts to safely meet the study goals will also be at the discretion of the investigator. Therefore, the risk for patients participating in this study and using daily doses of Soliqua 100/33 up to a maximum of 60 units of insulin glargine and 20 µg of lixisenatide is considered acceptable. All patients enrolled in this study will benefit from medical care and continuous monitoring of their glucose levels.

The important identified risks for Soliqua 100/33 are hypoglycemia or hyperglycemia associated with alterations in the insulin dosing regimen, hypersensitivity reactions, overdose due to medication errors, injection site reactions, and GI AEs, including nausea, diarrhea, and vomiting. This study proposes a titration algorithm with titration targets that will closely follow the US label for Soliqua 100/33 (Soliqua 2019), except in instances of hyper- or hypoglycemia, which require specific attention. All study participants will benefit from the safety monitoring planned during site visits as well as during the additional titration phone contacts.

Given the expected improvement of glycemic control and the additional measures to improve diabetes management, the benefits are considered to outweigh any potential risks associated with Soliqua 100/33. Therefore, the benefit-risk ratio for patients participating in Study LPS16990 is considered favorable.

2 Study Objectives, Estimands, and Endpoints

Objectives:

To determine the effect of Soliqua 100/33 on indices of glycemic control and variability, as measured via CGM, from baseline to Week 16, in insulin-naïve patients with very uncontrolled (HbA1c ≥9%-13%) T2DM.

2.1 Primary Efficacy Objective, Estimands, and Endpoints

The primary efficacy objective, estimand, and endpoint are presented in Table 2-1.

Table 2-1 Primary Efficacy Objective, Estimand, and Endpoint

Primary Objective	Primary Estimand Description	Primary Endpoint
• To demonstrate that in patients with T2DM failing to achieve glycemic control (HbA1c ≥9%-13%) on their current regimen of 2+ OADs with or without GLP-1 RAs, introduction of Soliqua 100/33 exhibits superiority in terms of time spent in range (70-180 mg/dL) at Week 16 compared with baseline, as measured by CGM	• The primary estimand is the mean change in the percentage of TIR (70-180 mg/dL) from baseline to Week 16. The primary estimand will be estimated based on the efficacy analysis set using obtained measurements, regardless of intercurrent events	• Change in the percentage of TIR (70-180 mg/dL) from baseline to Week 16

Abbreviations: CGM, continuous glucose monitoring; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug; T2DM, type 2 diabetes mellitus; TIR, time in range.

2.2 Key Secondary Efficacy Objectives and Endpoints

The key secondary efficacy objectives and endpoints are presented in Table 2-2.

Table 2-2 Key Secondary Efficacy Objectives and Endpoints

Key Secondary Objectives	Key Secondary Endpoints
• To evaluate the impact of Soliqua 100/33 on measures of glycemic control and variability in patients with T2DM	• Change (%) from baseline to Week 16 in CV • Change (mg/dL) from baseline to Week 16 in mean daily blood glucose • Change (mg/dL) from baseline to Week 16 in the maximum PPG exposure in the 4 hours after the breakfast meal • Change (%) from baseline to Week 16 in TAR (>180 mg/dL)

Abbreviations: CV, coefficient of variation; PPG, postprandial glucose; T2DM, type 2 diabetes mellitus; TAR, time above range.

2.3 Secondary, Other Efficacy, and Safety Objectives and Endpoints

The secondary, other efficacy, and safety objectives and endpoints are presented in Table 2-3.

Table 2-3 Secondary, Other Efficacy, and Safety Objectives and Endpoints

Objectives	Endpoints
Secondary	
• To evaluate the impact of Soliqua 100/33 on other measures of glycemic control and variability in patients with T2DM	• Proportion (%) of patients achieving CV <36% • Change (%) from baseline to Week 16 in TIR (70-180 mg/dL) for specific time blocks (6 am-12 pm, 12 pm-6 pm, 6 pm-12 am, and 12 am-6 am) • Proportion (%) of patients achieving GMI <7% and <9% at Week 16

Objectives	Endpoints
	• Change from baseline to Week 16 in the 4-hour PPG AUC_{0-4h} after start of the breakfast meal, including T_{max} • Proportion (%) of patients at Week 16 who spend <15 minutes/day at a glucose level <54 mg/dL
Other Efficacy	
• To evaluate the impact of Soliqua 100/33 on additional measures of glycemic control and variability in patients with T2DM	• Change (mg/dL) from baseline to Week 16 in MODD of glucose levels • Change (%) from baseline to Week 16 in TAR (>250 mg/dL) • Change (%) from baseline to Week 16 in TBR (<70 mg/dL) • Correlation of change in the percentage of TIR (70-180 mg/dL) and LS mean change in PRO from baseline to Week 16 • Correlation of percentage of TIR (70-180 mg/dL) and HbA1c percentage achieved at Week 16 • Correlation of patients reaching 60 units/day insulin glargine U100 and TIR >70% • Change in HbA1c percentage from baseline to Week 16
PRO	
• To assess patient-perceived treatment impact on HRQoL and treatment satisfaction	• Change from baseline to Week 16 in diabetes medication treatment satisfaction scores (total score and by subscales), using the DM-SAT questionnaire

Objectives	Endpoints
Safety	
• To assess the safety and tolerability of Soliqua 100/33	Safety evaluations will include evaluation of the following (for 16 weeks): • Overall hypoglycemia • Confirmed hypoglycemia o ADA Level 1: Measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) o ADA Level 2: Measurable glucose concentration <54 mg/dL (3.0 mmol/L) that needs immediate action o ADA Level 3: Severe event characterized by altered mental and/or physical functioning that requires assistance* from another person for recovery • AEs, SAEs, and AESIs

Abbreviations: ADA, American Diabetes Association; AE, adverse event; AESI, adverse events of special interest; AUC_{0-4h}, area under the concentration versus time curve from time 0 to 4 hours; CV, coefficient of variation; DM-SAT, Diabetes Medication Satisfaction Tool; GMI, Glucose Management Indicator; HbA1c, glycated hemoglobin; HRQoL, health-related quality of life; LS, least square; MODD, mean of daily difference; OAD, oral antidiabetic drugs; PPG, postprandial glucose; PRO, patient-reported outcome; SAE, serious adverse event; T2DM, type 2 diabetes mellitus; T_{max}, time to reach maximum concentration; TAR, time above range; TBR, time below range; TIR, time in range.

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

3 Investigational Plan

3.1 Study Design

This is a 16-week, multicenter, interventional, open-label, single-arm, Phase 4 study using blinded CGM (FreeStyle Libre Pro) to demonstrate improvement in the percentage of TIR from baseline in patients adding Soliqua 100/33 and treated for 16 weeks. The study will be conducted in approximately 100 patients whose T2DM is very uncontrolled on 2+ OADs with or without GLP-1 RAs (with stable doses for 3 months), as evident from a screening HbA1c of ≥9%-13%. The study will attempt to represent the diversity of the US patient population with T2DM **through site recruitment efforts**.

All eligible participants will undergo 14 days of blinded continuous CGM monitoring at baseline (the run-in period) and a mixed-meal tolerance test (MMTT) while on baseline medications. Soliqua 100/33 treatment will be initiated on Day 0 (Visit 3.2), after the MMTT (which is scheduled at Visit 3.1; Figure 3–1). Sulfonylurea (SU) doses should be down-titrated by 50% when starting Soliqua 100/33, and the last doses of daily dipeptidyl peptidase-4 inhibitor (DPP-4i) and daily GLP-1 RA (oral or injectable) should be administered on the morning of Day –1, the day before the first dose of Soliqua 100/33.

At Visit 3.1, participants on OADs or an oral or injectable GLP-1 RA will be required to take their dose after the blood sample for fasting plasma glucose (FPG) and HbA1c is collected and 30 minutes before administration of the meal during the MMTT (during which measures for both β-cell function and postprandial glucose [PPG] analyses will be captured). Participants on a weekly GLP-1 RA should have their baseline MMTT conducted within 7 (± 3) days after their last dose and administer their last weekly GLP-1 RA dose 7 (± 2) days before the first dose of Soliqua 100/33.

The dose of Soliqua 100/33 will be adjusted during the titration period (ie, from Weeks 1 through 12; Visits 4.0 to 5.4), at the investigator's discretion until the desired fasting SMPG value (80-100 mg/dL) is achieved.

During the end of the treatment period (from Visit 6 to Visit 7), participants will again be required to undergo 14 days of blinded continuous CGM monitoring and a MMTT (only to derive PPG measures). Soliqua 100/33 should be administered 30 minutes before

administration of the meal during the MMTT at Visit 7 (during which only measures for PPG analyses will be captured).

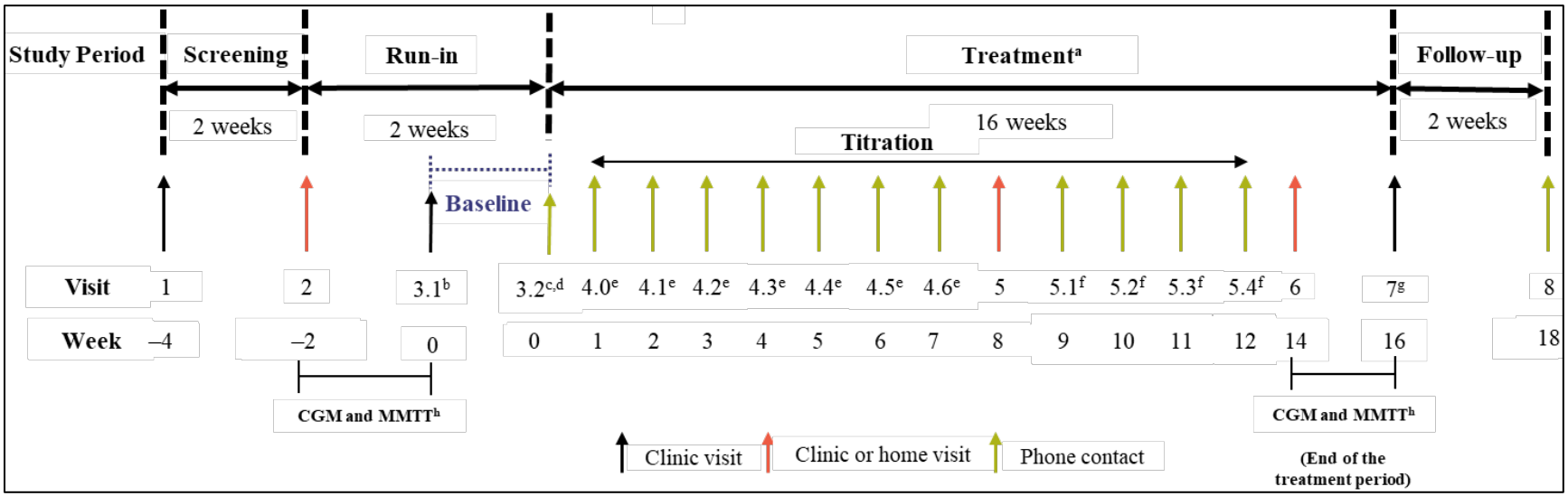
All participants will be allowed to continue their background OADs (except DPP-4i and SU, as previously described) at stable doses and regimens throughout the study period, unless they have to be stopped or modified for safety reasons.

Adverse events, including adverse events of special interest (AESIs), will be assessed. Physical examination (including body weight), hypoglycemia events, clinical laboratory values, and vital signs will be measured to evaluate the safety of the study drug treatments (Section 13.1).

The maximum study duration per participant will be 22 weeks. Three site visits, 3 site or home visits, and up to 13 phone contacts are scheduled.

Participants will have the choice to have Visits 2, 5, and 6 performed at the study site or at home. This choice is to be determined at the screening visit. Participants who opt for site visits should be encouraged not to change to home visits during the study period. However, if this is unavoidable, the home health provider and the sponsor-approved courier company for investigational medicinal product (IMP) shipment will need at least 72 hours' notice from the investigator to arrange a home visit and direct-to-patient (DTP) IMP supply, if required. An unscheduled site or home visit can be planned during the treatment period for IMP resupply, if required. If DTP Soliqua 100/33 supply is required, the sponsor-approved courier company will need at least 72 hours' notice to collect Soliqua 100/33 treatment kits from a study site.

Figure 3–1 Study Diagram



Abbreviations: CGM, continuous glucose monitoring; DPP-4i, dipeptidyl peptidase-4 inhibitor; DTP, direct-to-patient; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HCP, healthcare provider; IMP, investigational medicinal product; MMTT, mixed-meal tolerance test; SMPG, self-measured plasma glucose; SU, sulfonylurea.

Notes: During the run-in period, CGM device reinsertion will be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8; Section 6.2.1).

During the end of the treatment period, CGM device reinsertion will also be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8), if data can be captured during the 14-day end-of-treatment window (Section 6.2.1).

[a] An unscheduled visit can be planned anytime during the treatment period if IMP resupply is required. This can be a site visit or via phone contact with DTP IMP delivery. If DTP Soliqua 100/33 supply is required, the sponsor-approved courier company will need at least 72 hours' notice to collect Soliqua 100/33 treatment kits from a study site.

[b] Participants on weekly GLP-1 RA should administer their last dose 7 (± 2) days before the first dose of Soliqua 100/33, whereas the last dose of daily DPP-4i

and daily GLP-1 RA (oral or injectable) should be administered on the morning of Day –1, the day before the first dose of Soliqua 100/33.

[c] It is the first day of Soliqua 100/33 administration and includes a phone contact to ALL participants to ensure that all administration procedures were successfully executed and to answer any questions. The first day of Soliqua 100/33 administration (ie, Visit 3.2, Day 0) for participants on weekly GLP-1 RA will depend on their administration schedule and may not be the day immediately following Visit 3.1. Soliqua 100/33 administration for these participants should be 7 (± 2) days after their last weekly GLP-1 RA dose. A phone contact should be made to **participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation**, to remind them of the next morning's injection and to provide instructions for SoloStar pen use. The participants will provide their concomitant medication details to the site personnel over the phone.

[d] Doses of SU should be down-titrated by 50% when Soliqua 100/33 is started on Day 0.

[e] Weekly phone contacts for dose adjustments are to continue at the investigator's discretion until the desired fasting SMPG value is achieved.

[f] If the desired fasting SMPG value is not achieved in the first 8 weeks of treatment; the investigator has the option to continue weekly dose titration phone contacts for an additional 4 weeks (until Week 12) for the purpose of achieving glycemic targets.

[g] At the end of the study, participants should discuss with the investigator, in collaboration with their HCP, whether to continue on the Soliqua 100/33 treatment regimen or transition to an alternate antihyperglycemic therapy.

[h] At baseline, the CGM device will be removed and the data will be downloaded on Day –1 at their next site visit (ie, Visit 3.1), after collection of C-peptide, insulin, and plasma glucose data from the MMTT. Downloaded CGM data will be reviewed by the investigator to determine participants' study eligibility. NOTE: Participants on weekly GLP-1 RA should have their baseline MMTT conducted within 7 (± 3) days after their last dose. At the end of the treatment period, the CGM device will be removed and the data will be downloaded on the fifteenth day after CGM placement (ie, Visit 7; after collection of only plasma glucose data from the MMTT). Downloaded CGM data will be verified by the investigator at the site to determine participants' study completion.

3.1.1 Rationale of Study Design

This study is designed to demonstrate improvement in the percentage of TIR with Soliqua 100/33 in patients with very uncontrolled T2DM (HbA1c ≥9%-13%) after 3 months of stable treatment with 2+ OADs with or without additional GLP-1 RA therapy.

Continuous glucose monitoring has significantly improved the ability to monitor glycemic variability throughout the day. Data from CGM can be critical in making daily treatment decisions and quantifying TIR, which provides more actionable information than HbA1c alone (Battelino et al 2019). Continuous glucose monitoring is a much-improved measure of TIR compared with SMPG (ie, hundreds of values to analyze versus a single measure in time), to truly understand glycemic variability in people with T2DM.

In a previous post hoc analysis, treatment with Soliqua 100/33 improved measures of glycemic variability (ie, 7-point blood glucose data) in patients uncontrolled on either oral or insulin therapies more than its individual components (ie, lixisenatide or insulin glargine U100). This finding was attributed to the complementary reductions of both fasting and postprandial hyperglycemia (Aronson et al 2019). Clinicians frequently request CGM measures to better understand their patients' TIR, time above range (TAR), and time below range (TBR). Hence, the current study is intended to replicate and enhance the results from the 7-point blood glucose study, but using CGM. Measures such as TIR, coefficient of variation (CV), TAR, TBR, and PPG will be collected in this patient population with very high HbA1c. This is the first CGM study performed with Soliqua 100/33 in patients with very uncontrolled T2DM (HbA1c ≥9%-13%) on oral therapies with or without GLP-1 RAs.

3.1.2 Duration of Study Participation for Each Participant

The study comprises the following periods (further detailed in the graphical study diagram [Figure 3–1] and the schedule of events [SoE; Section 13.1]):

- A screening period of up to 2 weeks.
- A run-in period of 2 weeks, including the baseline period.
    - At Visit 2, the CGM device will be applied to the back of the upper arm of the participant and baseline CGM data will be collected continuously for 14 days; the

device will be removed at the subsequent site visit during the baseline period (ie, Visit 3.1), after the MMTT.

- During the baseline period, on Day –1 (Visit 3.1), participants will return to the site for the MMTT (for both β-cell function and PPG measures) and CGM removal and data download (after the MMTT). Dispensing of the Soliqua 100/33 pen and instruction on administration of Soliqua 100/33 will also take place during this visit.
- Visit 3.2 (ie, Day 0) during the baseline period is the first day of Soliqua 100/33 administration and includes a phone contact to ALL participants to ensure all administration procedures were successfully executed and to answer any questions. (Note: The first day of Soliqua 100/33 administration [ie, Visit 3.2, Day 0] for participants on weekly GLP-1 RA will depend on their administration schedule and may not be the day immediately following Visit 3.1. Soliqua 100/33 administration for these participants should be 7 [± 2] days after their last weekly GLP-1RA dose.)
  - **A phone contact should** also be made **ONLY to participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation,** to remind them of the next morning's injection and to provide instructions for SoloStar pen use. The participants will provide their concomitant medication details to the site personnel over the phone.

- A 16-week open-label treatment period.
  - Visit 3.2 (ie, Day 0) is the first day of Soliqua 100/33 administration and begins the open-label treatment period (with different initiation requirements based on weekly or daily GLP-1 RA use, as explained above).
  - The dose of Soliqua 100/33 will be adjusted during the titration period (ie, from Weeks 1 through 12; Visits 4.0 to 5.4), at the investigator's discretion, until the desired fasting SMPG value (80-100 mg/dL) is achieved (Table 5-1).
  - During Visits 4.0 to 4.6, weekly phone contacts for dose adjustments are to continue at the investigator's discretion until the desired fasting SMPG value is achieved.
  - If the desired fasting SMPG value is not achieved in the first 8 weeks of treatment, the investigator has the option to continue weekly dose titration phone contacts for an additional 4 weeks (until Week 12; ie, from Visits 5.1 to 5.4) with the purpose of achieving glycemic targets.

- At Visit 6, a blinded CGM device will again be applied to the back of the upper arm of the participant, and CGM data will be collected continuously for 14 days; the device will be removed at the subsequent site visit (ie, Visit 7), after the MMTT (only to derive PPG measures).
- At the end of the study (ie, Visit 7), participants should discuss with the investigator, in collaboration with their HCP, whether to continue on the Soliqua 100/33 treatment regimen, or transition to an alternate antihyperglycemic therapy.

- A 2-week post-treatment safety follow-up period after the last dose of Soliqua 100/33 (eg, treatment completion) or after premature/permanent treatment discontinuation from Soliqua 100/33.

The total duration of the study will be approximately 22 weeks for each participant.

A detailed description of the assessments performed during each study period and at each visit is provided in Section 13.1.

3.1.3 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

4 Selection of Study Population and Discontinuation/Withdrawal

One-hundred participants will be enrolled at approximately 15 sites in the US. Participants will be enrolled in the study only if they meet all of the inclusion criteria and none of the exclusion criteria.

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

4.1 Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent, provides signed written informed consent, is willing and able to complete the electronic diary (eDiary), and agrees to comply with protocol requirements (confirmed by the site staff performing the recruitment efforts).
2. Is an adult ≥18 years of age.
3. Has an HbA1c ≥9%-13% during the run-in period.
4. Was diagnosed with T2DM at least 6 months before the baseline period.
5. Has been treated with 2+ OADs with or without GLP-1 RAs with stable doses (for both) for 3 months before the screening period.
6. Is willing and able to wear the CGM device continuously for 14 days to capture CGM measures at baseline (from Visit 2 [ie, the run-in period] until the next site visit at Visit 3.1) and again at the end of the treatment period [ie, from Visit 6 until the next site visit at Visit 7; Section 13.1).
7. Is willing and able to prick fingers a minimum of 2 to 4 times per week, using sterile lancets provided with a manual blood glucose meter kit.
8. Is willing to discontinue daily (oral or injectable) or weekly GLP-1 RA or DPP-4i before administration of Soliqua 100/33.

9. Is willing and able to inject Soliqua 100/33 and increase dose as needed to achieve SMPG target.

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

    - Is a woman of non-childbearing potential (WONCBP), as defined in contraceptive and barrier guidance (Section 13.7).
    - Is a woman of childbearing potential (WOCBP) and agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in contraceptive and barrier guidance (Section 13.7), during the study treatment period (to be effective before starting the study drug) and for at least 1 week after the last administration of study drug.
        - A WOCBP must have a negative urine pregnancy test at both screening and baseline visits. (Note: If a urine test cannot be confirmed as negative [eg, an ambiguous result], a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.)

4.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Has T1DM or any other types of diabetes except T2DM.

2. Is being treated with meglitinides (eg, nateglinide, repaglinide).

3. Has a body mass index (BMI) >40 kg/m² during the screening period.*

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

4. Provides less than equivalent of 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period (eg, days of CGM device wear × % time CGM device active < 8; Section 6.2.1).

5. Has any current or previous skin conditions, including (but not limited to) severe psoriasis, burns, eczema, scarring, and excessive tattoos, that would inhibit proper wearing of the CGM device.

6. Has a history of severe nausea and vomiting that resulted in discontinuation of GLP-1 RA.

7. Has a known history or presence of clinically significant pancreatitis or gastroparesis.

8. Has had an episode of severe hypoglycemia or hypoglycemia unawareness (defined as the onset of neuroglycopenia before the appearance of autonomic warning symptoms [for example, blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion] or as the failure to sense a significant fall in blood glucose below normal levels) within the 6 months before the screening period.

9. Has any clinically significant abnormality identified from the physical examination, vital sign measurements, or laboratory tests (eg, amylase, lipase, alanine aminotransferase [ALT] >3 × upper limit of normal [ULN], calcitonin ≥20 pg/mL, severe renal impairment [estimated glomerular filtration rate, <30mL/min/1.73m^2], or end stage renal disease) or visual impairment at screening that, in the opinion of the investigator or any qualified designee, would make implementation of the protocol or interpretation of the study results difficult or would preclude safe participation in the study.

10. Has personal or immediate family history of medullary thyroid cancer (MTC) or a genetic condition that predisposes the participant to MTC (eg, multiple endocrine neoplasia syndromes).

11. Has current or known history of alcohol or drug abuse within 6 months before the screening period.

12. Has significant current (within past 2 months) or expected use of medications known to affect glycemia (eg, ≥5 mg/day prednisone).

13. Uses substances known to interfere with CGM readings, such as aspirin-containing products (>650 mg/day of salicylic acid) or supplements containing vitamin C (>1000 mg/day of ascorbic acid) taken during the 14-day periods of CGM measure at baseline (ie, Visit 2 to Visit 3.1) and the end of the treatment period (ie, Visit 6 to Visit 7).

14. Has undergone previous treatment with any insulin (except for short-term treatment due to intercurrent illness, including gestational diabetes, at the discretion of the investigator).

15. Is enrolled in another clinical study or has taken other investigational drug(s) within 1 month or 5 half-lives from screening, whichever is longer.

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

17. Is an employee or family member of the investigator or study site personnel.

18. Is not suitable for participation, whatever the reason, as judged by the investigator, including medical or clinical conditions, or potentially is at risk of noncompliance to study procedures.

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

20. Has a hypersensitivity to Soliqua 100/33, either of its active components (insulin glargine or lixisenatide), or any of its excipients that, in the opinion of the investigator, contraindicates participation in the study.

21. Has used weight loss drugs (including over-the-counter [OTC] and herbal medications) within 12 weeks before the screening visit.

4.3 Screen Failure

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting to meet Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse events (SAEs).

Participants who are screen failed may be rescreened based on a discussion between the medical monitor and the investigator.

4.4 Discontinuation From Study Treatment and/or Withdrawal From the Study

4.4.1 Discontinuation From Study Treatment

4.4.1.1 Permanent Discontinuation

All efforts should be made to keep participants on treatment.

In rare instances, it may be necessary for a participant to permanently discontinue study treatment. Before permanent discontinuation of treatment regardless of the reason or as soon as possible after the decision for discontinuation has been made, if possible, the participant will undergo all procedures planned for the last dosing day with Soliqua 100/33 and the follow-up visit (Section 13.1).

All cases of permanent treatment discontinuation (Section 4.4.3) must be recorded by the investigator in the appropriate pages of the electronic case report form (eCRF) when confirmed.

4.4.1.2 Temporary Discontinuation

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

Temporary study drug discontinuation may be considered by the investigator because of suspected AEs or for other reasons. In case of study drug interruption due to an AE, reinitiating Soliqua 100/33 treatment at the appropriate dose will be done under close and appropriate clinical/and or laboratory monitoring if the investigator deems the relationship of the event to Soliqua 100/33 as unlikely and if the study inclusion criteria are still met.

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

4.4.2 Lost to Follow-up

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

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

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

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. The methods to contact the participants include 2 phone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record.

If the participant continues to be unreachable, they will be considered to have withdrawn from the study.

4.4.3 Handling of Withdrawals

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

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

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

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

A participant may withdraw from the study or study treatment under the circumstances (including, but not limited to) listed below:

- The participant intends to become pregnant.
- The participant may be withdrawn at the discretion of the investigator due to noncompliance or due to a safety concern.
- The participant will be withdrawn if starting any drugs that interfere with glucose metabolism (eg, steroid doses equivalent to prednisone ≥5 mg/day).
- The participant may be withdrawn if diagnosed with acute pancreatitis (defined as meeting 2 of the following 3 rules: typical abdominal pain; amylase/lipase >3 × ULN; and/or characteristic ultrasound, computed tomography, or magnetic resonance imaging findings).
- If the fasting or the mean SMPG value during 3 consecutive days is >300 mg/dL, the investigator will schedule an unplanned visit as soon as possible to obtain confirmatory FPG and investigate the cause. If no apparent or intercurrent cause is detected, the participant may be withdrawn.
- The participant has recurrent severe hypoglycemia or recurrent nocturnal hypoglycemia during the treatment period that poses a potential risk to the participant, as judged by the investigator.
- The participant is unable to comply with the study protocol, at the investigator's discretion.

Whenever possible, all participants who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study and follow-up assessments. Participants who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

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

It is vital to obtain follow-up data on any participant who is withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety, and follow-up procedures.

4.4.4 Replacements

Participants who discontinue the study will not be replaced.

5 Study Treatments

5.1 Study Drug

- Formulation: Soliqua 100/33 will be supplied as a sterile, non-pyrogenic, clear, colorless solution in a SoloStar™ prefilled (disposable) pen for subcutaneous (SC) injection. The SoloStar pen is necessary for Soliqua 100/33 administration, and it is considered as an integral part of Soliqua 100/33 therapy.
    - The prefilled SoloStar disposable pen contains 3 mL of sterile solution containing 100 units/mL insulin glargine and 33 µg/mL lixisenatide in a 3:1 ratio (ie, 3 units of insulin glargine to 1 µg lixisenatide).
    - The pen allows for administration of both ingredients simultaneously with doses ranging from 15 units/5 µg to 60 units/20 µg (insulin glargine U100/lixisenatide).
    - Soliqua pen instructions will be given to all participants at Visit 3.1.
    - A phone contact should be made **to participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation,** to remind them of the next morning's injection and to provide instructions for SoloStar pen use.
- Route of administration: SC injection using the SoloStar pen into the abdominal area, thigh, or upper arm. Injection sites should be rotated within the same region from one injection to the next to reduce the risk of lipodystrophy.

5.2 Non-Investigational Medicinal Product

The protocol-mandated background OADs (Section 5.2.1) are considered non-investigational medicinal product (NIMP).

5.2.1 Background OADs Related to Glycemic Management

The following oral classes of medication related to glycemic management are permitted during the screening and treatment periods of the study, initiated and at stable doses for a minimum of 3 months before the screening period:

- SU (which will be down-titrated by 50% when starting Soliqua 100/33 on Day 0).

- Biguanides.
- Thiazolidinediones.
- α-glucosidase inhibitors.
- Sodium-glucose co-transporter-2 (SGLT2) inhibitors.
- Bile acid sequestrants.
- Dopamine agonists.

5.2.2 Appropriate Corrective Action/Rescue Therapy

Titration will be exceedingly important throughout the first 12 weeks of this study and will require consistent reviews of fasting SMPG values, the daily insulin dose, and hypoglycemia events to identify participants whose Soliqua 100/33 dose is not being appropriately managed.

If after Week 12 (ie, end of the titration period), the participant's FPG level is >240 mg/dL with no reasonable explanation for severe hyperglycemia, such as intercurrent illnesses or nonadherence to instructed titration, the investigator should obtain an HbA1c measurement and decide whether rescue therapy is warranted.

5.3 Storage and Dispensing

Before first use, the Soliqua 100/33 pen should be stored in a refrigerator from 36°F to 46°F (2°C to 8°C) and protected from light and must **not** be frozen. Pens are to be discarded only after accountability and reconciliation is performed by PPD's clinical research associate (CRA) and after the expiration date printed on the label. All pens in the same kit should have the same expiration date; therefore, pens from the same kit should be stored separately (eg, the pen currently being utilized should be stored at room temperature, whereas the other non-utilized pens should be stored in the refrigerator). The site should contact PPD for further instructions or notification if the expiration date of a pen/kit is near (eg, for possible re-labeling; do not automatically discard any pens/kits). Expired kits or pens should not be provided to participants.

The Soliqua 100/33 pen should not be stored in the freezer and should not be frozen. The Soliqua 100/33 pens should be separated (from the kit and any other pens) and stored (either at **room temperature** if the pen is in use, or in the **refrigerator** if not yet used) and should **not be used** if frozen or previously frozen. The site should not discard any Soliqua 100/33 pens or the kit until reconciliation and accountability is performed by the CRA.

After first use, the Soliqua 100/33 pen should be stored at room temperature below 77°F (25°C). The pen cap should be replaced after each use to protect it from light. The participant should keep any empty pens in the kit box to be returned to the site during the next site visit. Each pen should be replaced with a new pen 28 days after first use.

The pen needle should be removed after each injection and discarded, and the Soliqua 100/33 pen should be stored at room temperature without a needle attached. This type of storage should prevent infection and/or contamination or leakage of the Soliqua 100/33 pen and will ensure accurate dosing. A new needle should always be used for each injection to prevent infection and/or contamination.

5.4 Method of Assigning Participants to Treatment Groups

Not applicable. This is an open-label, single-arm study.

5.5 Treatments Administered

- Time of administration:
    - Soliqua 100/33 should be self-administered once-daily in the morning approximately 60 minutes before breakfast.
    - The first dose of Soliqua 100/33 will be administered on the morning of Day 0 (ie, Visit 3.2). This date should be 7 [± 2] days after the last weekly GLP-1 RA dose or the morning following the last dose of DPP-4i or daily GLP-1 RA (oral or injectable) administration.

Starting dose

- For all participants, the starting dose of Soliqua 100/33 will be 15 units of insulin glargine (corresponding to 5 µg of lixisenatide).

- The maximum daily dose of Soliqua 100/33 should not exceed 60 units of insulin glargine (corresponding to 20 µg of lixisenatide).

5.5.1 Dose Modifications

The dose of Soliqua 100/33 will be adjusted with the aim of attaining a target fasting SMPG value of 80 to 100 mg/dL (Table 5-1). The dose will be adjusted based on the lowest fasting SMPG values in conjunction with measurements from the previous 3 days throughout the study period. During the titration period (ie, Weeks 1 through 12), fasting SMPG should be assessed on each of the 3 to 4 days before each dose adjustment. During the titration period, the dose of Soliqua 100/33 should be adjusted upwards or downwards by 2 to 4 units every week (with additional titration also at the discretion of the investigator in accordance with the participant's blood glucose monitoring result), with the objective of safely attaining a fasting SMPG level of 80 to 100 mg/dL, as well as other glycemic targets, while minimizing the risk of hypoglycemia and hyperglycemia), at the investigator's discretion. The duration of the titration period and number of phone contacts to meet the study goals will also be at the discretion of the investigator.

As stated above, dose titration will be at the investigator's discretion and guided by the recommended dose adjustment algorithm with the objective of safely attaining a fasting SMPG value of 80 to 100 mg/dL (Table 5-1). Study participants should be trained and retrained on an ongoing basis to establish proper understanding of titration procedures because very close communication between the participant and the study site is necessary to ensure adequate titration while minimizing the associated risks. Investigators may adjust or stop titration or temporarily reduce the dose if they believe further titration would result in participants experiencing any AEs (eg, hypoglycemia, AESIs). After the target fasting SMPG value has been achieved, the dose of Soliqua 100/33 should be adjusted as necessary until the end of the study to maintain the target fasting SMPG value in accordance with the dose titration guidelines provided in Table 5-1. If the desired fasting SMPG target is not achieved in the first 8 weeks of treatment, the investigator has the option to continue weekly dose titration phone contacts for an additional 4 weeks (until Week 12) for the purpose of achieving glycemic targets.

Doses will be adjusted at least weekly, but additional titration may be considered at the investigator's discretion. Participants are, therefore, required to record their fasting SMPG

values before breakfast at least 3 to 4 times per week throughout the study period to inform each dose adjustment.

Table 5-1 Recommended Dose Adjustment Algorithm for Soliqua 100/33

Median of Fasting SMPG Values (With Lowest Value Considered in Conjunction With Previous 3 Measurements)	Soliqua 100/33 Dosage Adjustment (Units/Week)
>140 mg/dL (>7.8 mmol/L)	+4 units
>100 to ≤140 mg/dL (>5.5 to ≤7.8 mmol/L)	+2 units
Glycemic target: 80 to 100 mg/dL (4.4-5.5 mmol/L), inclusive	No change
≥60 to <80 mg/dL (≥3.3 to <4.4 mmol/L)	–2 units
<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemia events or 1 severe hypoglycemia event (requiring assistance) documented in the preceding week	–2 to –4 units or at the discretion of the investigator or any qualified designee

Abbreviation: SMPG, self-measured plasma glucose.

Notes: Dose changes should also be based on the median SMPG values (with the lowest value considered in conjunction with the previous 3 measurements). If the lowest value from the previous 3 measurements is from 80 to 100 mg/dL and the other 2 values are well above 100 mg/dL, further titration may be implemented at the investigator's discretion. If the lowest value is <70 mg/dL and the other 2 values are near 100 mg/dL, the investigator may stop or temporarily reduce the dose if, in their judgment, further titration would be hazardous.

5.6 Identity of Investigational Product

Soliqua 100/33 (insulin glargine/lixisenatide) is a sterile, non-pyrogenic, clear, colorless solution in a SoloStar prefilled (disposable) pen for SC injection.

Sanofi will provide adequate supplies of Soliqua 100/33 pen to the sites directly.

The following drug supplies will be used in the study:

Product	Supplied as:
Soliqua 100/33	SoloStar pens (containing a 3 mL of sterile solution of insulin glargine 100 units/mL and lixisenatide 33 µg/mL)

5.7 Management of Clinical Supplies

5.7.1 Study Drug Packaging and Storage

Soliqua 100/33 is an injection supplied as a sterile, clear, colorless solution in a 3 mL, prefilled, disposable, single-patient-use pen injector and is shipped by Sanofi. Soliqua 100/33 SoloStar pens will be supplied as open-label treatment kits. Packaging will be in accordance with the administration schedule. The content of the labeling will be in accordance with the local regulatory specifications and requirements. The appropriate number of kits (including pen needles as ancillary supplies) will be dispensed to provide participants with Soliqua 100/33 coverage up to the next site visit or phone contact with DTP Soliqua 100/33 delivery (Section 13.1).Storage conditions and use-by-end date (ie, expiry date) are part of the Soliqua 100/33 label text.

Investigators or other authorized persons (eg, pharmacists, IMP managers) are responsible for storing Soliqua 100/33 in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures. Control of Soliqua 100/33 storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling Soliqua 100/33 should be managed according to the rules provided by the sponsor.

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

5.7.2 Study Drug Accountability

The investigator or other personnel designated by the investigator will maintain accurate records of receipt of study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each participant

in the study. The investigator or other personnel designated by the investigator will also be responsible for controlling the site stocks of Soliqua 100/33 and requesting any resupply, as needed. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

All Soliqua 100/33 will be dispensed in accordance with the investigator's oversight. It is also the investigator's responsibility to ensure that an accurate recording of Soliqua 100/33 kits issued and returned is maintained.

Any quality issue noticed with the receipt or use of Soliqua 100/33 pen (deficiency in condition, appearance, documentation, labeling, expiration date, etc.) must be promptly reported to the sponsor. Some deficiencies may be recorded through a complaint procedure (Section 6.3.7).

A potential defect in the quality of the Soliqua 100/33 pen may prompt initiation of a recall procedure by the sponsor. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor, in order to recall the Soliqua 100/33 pens and eliminate potential hazards.

Under no circumstances will the investigator supply Soliqua 100/33 pens to a third party, (except for DTP shipment, for which a courier company has been approved by the sponsor), allow the Soliqua 100/33 pen to be used other than as directed by this clinical study protocol, or dispose of the Soliqua 100/33 pen.

5.7.3 Other Supplies

5.7.3.1 Blood Glucose Meter Kit

Each study participant will be provided with a blood glucose meter kit, in order to perform SMPG assessments. The blood glucose meter kit will include a blood glucose meter, lancing device, test strips, sterile lancets, storage box, control solution, and instructions for use.

5.7.3.2 CGM Device (FreeStyle Libre Pro Flash Glucose Monitoring System)

The FreeStyle Libre Pro Flash Glucose Monitoring System (Abbott Laboratories) is a professional CGM device indicated for detecting trends and tracking patterns in people with diabetes (aged ≥18 years). The system automatically captures the glucose concentration in the interstitial fluid every minute. It also automatically records the glucose concentration every 15 minutes, storing that data in a rolling 8-hour log. The system has 3 main parts: a disposable sensor, a handheld reader, and FreeStyle Libre Pro software. Participants will not have access to the reader or software (these will remain with the investigator) and therefore will remain blinded to the data.

The device will be applied to the back of the upper arm of each participant, and they will be required to wear it continuously for 14 days during CGM data collection at baseline (during the run-in period) and for 2 weeks at the end of the treatment period (ie, Weeks 14 to 16). The device does not require user calibration with blood glucose values.

Clinical sites and participants will be provided with device adhesion guidance, including proper skin preparation and products to increase adhesion (TORBOT SKIN TAC™, a latex-free “tacky” skin barrier, and MASTISOL LIQUID ADHESIVE®, a clear, non-irritating liquid adhesive that secures dressings). Clinical sites will be thoroughly trained on the device adhesion guidance as well as the checks that must be performed to ensure that the devices are fully functioning before a participant leaves the site.

5.8 Overdose Management

An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the investigator or spontaneously reported by the participant and is defined as any dose administration that, in the investigator’s opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin or is at least twice the intended dose within the intended therapeutic interval. Any overdose, with or without associated AEs, must be promptly reported in eCRFs by the sites, which will then be notified to the sponsor’s representative (ie, PPD Pharmacovigilance). Overdoses without signs or symptoms should be recorded as a standard overdose; any AEs associated with the overdose should be reported on the relevant AE/SAE sections in the eCRF.

5.8.1 Treatment of Overdose

Insulin Glargine

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in study drug dose, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

Lixisenatide

During clinical studies, doses up to 30 µg of lixisenatide twice daily (3 times the daily recommended dose) were administered to patients with T2DM in a 13-week study. Increased incidence of GI disorders was observed (Soliqua 2019).

In case of overdose, appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms, and the Soliqua 100/33 dose should be reduced to the prescribed dose.

5.9 Blinding

Not applicable. This is an open-label, single-arm study.

5.10 Treatment Accountability and Adherence

Measures taken to ensure and document treatment adherence and IMP accountability include the following:

- The treatment kit number should be properly recorded as required on the appropriate eCRF page, for accounting purposes.
- All medication treatment kits (whether empty or unused) are to be returned by the participant at each visit when treatment dispensing is planned.

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

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

- The monitor in charge of the study will check the data entered on the Soliqua 100/33 administration page of the eCRF and compare them with the Soliqua 100/33 study drug that has been returned and the participant's treatment log form.

5.11 Concomitant Therapy

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

The participants should be reminded that vitamin C alone, supplements containing vitamin C with >1000 mg of ascorbic acid, aspirin alone, or aspirin-containing products with >650 mg of salicylic acid will interfere with CGM readings and should not be taken during the 14-day periods of CGM measure (ie, at baseline [from Visit 2 to Visit 3.1] and the end of the treatment period [from Visit 6 to Visit 7]). Additionally, medications known to affect glycemia, such as ≥5 mg/day of prednisone should be prohibited during this 16-week study period. Participants on meglitinides (eg, nateglinide, repaglinide) or weight loss drugs should also be prohibited from inclusion into the study.

Any concomitant medication deemed necessary for the welfare of the participant during the study may be given at the discretion of the investigator. However, the investigator is responsible for ensuring that details regarding the medication are recorded in full in the eCRF. The Soliqua 100/33 label should be consulted for any additional information regarding concomitant medication administration.

6 Study Assessments and Procedures

Before performing any study procedures, all potential participants will sign an informed consent form (ICF). Participants will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the participant. The investigator will also sign the ICF.

6.1 Study Visits

The SoE is detailed in Section 13.1.

- The screening period (Visit 1) will encompass up to 2 weeks and includes the following:
  - Obtaining informed consent.
  - Eligibility criteria.
  - Demographic assessment.
  - Review of medical/surgical history and current medications.
  - Physical examination (BMI calculation), dispensing of glucometer, HbA1c measurement, and setting up the eDiary.
  - Recording of vital signs, and clinical chemistry, calcitonin, hematology, urinalysis, and pregnancy tests.
- The run-in period (Visit 2) will encompass 2 weeks, including the baseline period, and includes HbA1c measurement and application of blinded CGM device (FreeStyle Libre Pro).
  - Visit 3.1 will be a site visit and includes assessment of eligibility criteria, MMTT, CGM device removal and data download (after the MMTT), CGM compliance assessment, evaluation of PPG and biomarkers of β-cell function (insulin, C-peptide, plasma glucose) during the MMTT, instructions for certain therapies (eg, DPP-4i, oral daily or weekly GLP-1 RA, and down-titration of SU by 50% when starting Soliqua 100/33), dispensing of Soliqua 100/33 and providing instructions for SoloStar pen use HbA1c and FPG measurements, administration of the Diabetes Medication Satisfaction Tool (DM-SAT), recording of vital signs and body weight, and clinical chemistry, hematology, urinalysis, and pregnancy tests.

- Visit 3.2 (ie, Day 0) during the baseline period is the first day of Soliqua 100/33 administration and includes a phone contact to ALL participants to ensure that all administration procedures were successfully executed and to answer any questions. (Note: The first day of Soliqua 100/33 administration [ie, Visit 3.2, Day 0] for participants on weekly GLP-1 RA will depend on their administration schedule and may not be the day immediately following Visit 3.1. Soliqua 100/33 administration for these participants should be 7 [± 2] days after their last weekly GLP-1 RA dose.)
  - **A phone contact should** also be made **ONLY to participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation,** to remind them of the next morning's injection and to provide instructions for SoloStar pen use. The participants will provide their concomitant medication details to the site personnel over the phone.

- The treatment period will encompass up to 16 weeks (Visits 3.2 through 7) and includes the following:
  - Visit 3.2 (ie, Day 0) is the first day of Soliqua 100/33 administration and begins the open-label treatment period (with different initiation requirements based on weekly or daily GLP-1 RA use, as explained above).
  - Titration period (Visits 4.0 to 4.6, 5, and 5.1 to 5.4).
    - For Visits 4.0 to 4.6, titration of the Soliqua 100/33 dose will occur via phone contacts, but it can occur at the study site or at home for Visit 5. For Visits 5.1 through 5.4, titration of Soliqua 100/33 dose will again occur via phone contacts.
    - During the titration period, participants will continue to make entries into their eDiary, administer Soliqua 100/33, adjust the Soliqua 100/33 dose, and capture any product complaints.
    - Other than an unscheduled visit, dispensing of Soliqua 100/33 will occur at Visit 5, if required. A pregnancy test will be conducted at Visit 5.
  - Visit 6:
    - Application of blinded CGM device and assessment of Soliqua 100/33 adherence.
    - Capturing of any product complaints.

- Visit 7 (ie, end of the treatment period):
  - Physical examination (including body weight), MMTT (only to derive PPG measures), removal of CGM device and download of data, and assessment of Soliqua 100/33 adherence.
  - HbA1c and FPG measurements and recording of the DM-SAT.
  - Vital signs and clinical chemistry, hematology, urinalysis, and pregnancy tests.
- At the end of the study (ie, Visit 7), participants should discuss with the investigator, in collaboration with their HCP, whether to continue on the Soliqua 100/33 treatment regimen or transition to an alternate antihyperglycemic therapy.

- An unscheduled visit can be performed at any time during the treatment period and may include the following:
  - Dispensing and adjustment of Soliqua 100/33 dose.
  - Review of concomitant medications.
  - Recording of hypoglycemia events and AEs/SAEs (including AESIs).
- The follow-up safety period (Visit 8) will occur 2 weeks after the end of the treatment period.

- Fasting SMPG values and those measures required to manage hypoglycemia events will occur from the run-in period (Visit 2) through the end of the treatment period (Visit 7).

- Soliqua 100/33 dosing will occur from the end of the baseline period (Visit 3.2) through the end of the treatment period (Visit 7).

- eDiary completion, recording of hypoglycemia events, and AEs/SAEs (including AESIs) will occur from the screening period (Visit 1) through the follow-up period (Visit 8), whereas review of concomitant medications will occur from the baseline period (Visit 3.1) through the follow-up period (Visit 8).

6.2 Efficacy Assessments

6.2.1 CGM Measures

Blinded CGM will be performed for 14 continuous days during baseline (ie, from Visit 2 to Visit 3.1) and again for 14 days at the end of the treatment period (ie, from Visit 6 to Visit 7; Section 13.1). The baseline CGM measure will be captured before discontinuing the daily (oral or injectable) or weekly GLP-1 RA, DPP-4i, or down-titration of SU by 50%, and before initiation of Soliqua 100/33 treatment. The blinded CGM device (FreeStyle Libre Pro) will be applied to the back of the upper arm of the participant and activated at Visit 2 (ie, the run-in period). Participants will be required to wear the device continuously for 14 days for baseline CGM data collection, with device removal and data download on Day –1 at their next site visit during the baseline period (ie, Visit 3.1), after collection of C-peptide, insulin, and plasma glucose data from the MMTT. Downloaded CGM data will be reviewed by the investigator to determine the participants' study eligibility. (Note: During the run-in period, CGM device reinsertion will be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data [not necessarily consecutive] over a 14-day period as a result of premature sensor failure [eg, days of CGM device wear × % time CGM device active < 8].) Similarly, participants will be required to continuously wear the device for 14 days at the end of the treatment period from Weeks 14 to 16 (ie, Visit 6 to Visit 7) to collect CGM data, with device removal and data download on the fifteenth day after CGM placement (ie, Visit 7), after collection of only plasma glucose data from the MMTT. Downloaded CGM data will be verified by the investigator at the site to determine participants' study completion. During the end of the treatment period, CGM device reinsertion will also be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8), if data can be captured during the 14-day end of treatment window. (Note: The minimum requirement for evaluable CGM data is if at least 10 out of 14 days [not necessarily consecutive] have at least ≥80% of evaluable CGM data per 24-hour period during the run-in period as well as the end of the treatment period [ie, from Weeks 14 to 16]; Battelino et al 2020.) Criteria for CGM device reinsertion are provided in Table 6-1 and Figure 6–1. Any combination of number of days of CGM device worn and % time CGM device is active (Table 6-1) that results in fewer than 8 equivalent days (defined as ineligibility) of evaluable

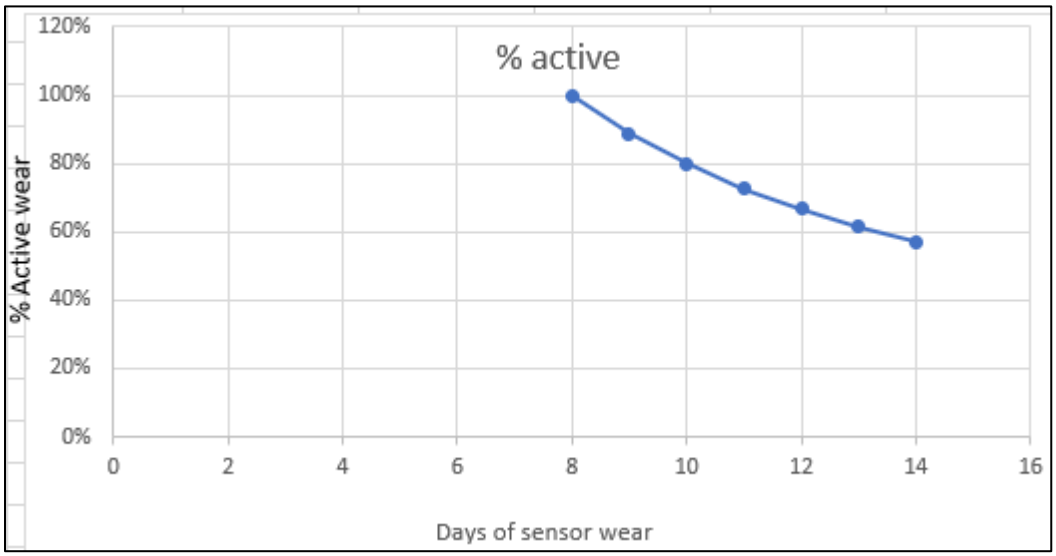
CGM data will require device reinsertion. Eligibility and analysis criteria for CGM measures are provided in Section 13.9.

Table 6-1 Criteria for CGM Device Reinsertion

No. of Days CGM Device Worn[a]	Time CGM Device Active (%)[a]	Equivalent Days
8	100	8.00
9	89	8.01
10	80	8.00
11	73	8.01
12	67	8.04
13	62	8.01
14	57	7.98

Abbreviations: AGP, Ambulatory Glucose Profile; CGM, continuous glucose monitoring.
[a] AGP report.

Figure 6–1 Criteria for CGM Device Reinsertion



Abbreviation: CGM, continuous glucose monitoring.

Participants with less than equivalent of 8 days of evaluable CGM data (not necessarily consecutive) of a 14-day period (eg, days of CGM device wear × % time CGM device active < 8) during the run-in period will be considered as screen failures. For participants

who discontinue study treatment prematurely, the visit window can be extended by 14 days to collect the CGM data before they permanently discontinue the treatment.

6.2.2 MMTT-Derived β-Cell Function and PPG Measures

Participants will undergo the MMTT (while wearing the CGM device) to assess maximum PPG exposure in the 4-hour period after the breakfast meal (tested at a central laboratory) with biomarkers of β-cell function (plasma glucose, insulin, and C-peptide) measured at Visit 3.1 (ie, site visit during the baseline period). The baseline MMTT will be conducted before discontinuing the daily (oral or injectable) or weekly GLP-1 RA, DPP-4i, or down-titration of SU by 50%. At Visit 3.1, participants on OADs or an oral or injectable GLP-1 RA will be required to take their dose after the blood sample for FPG and HbA1c is collected and 30 minutes before administration of the meal during the MMTT. Participants on weekly GLP-1 RA should have their baseline MMTT conducted within 7 (± 3) days after their last dose. During baseline (Visit 3.1), blood samples will be collected at the following time points: premeal (30 min) and just before administration of OADs or GLP-1 RA (oral or injectable) (baseline); time 0 (just before meal administration), 10 min, 20 min; and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 hours post-meal for plasma glucose, C-peptide, and insulin levels.

At the end of the treatment period (Visit 7), participants will again undergo the MMTT (while wearing the CGM device; only to derive PPG measures). Soliqua 100/33 should be administered 30 minutes before administration of the meal during the MMTT at Visit 7. At the end of the treatment period (Visit 7), blood samples will be collected for plasma glucose levels, as follows: premeal (30 min) and just before administration of Soliqua 100/33; and time 0 (just before meal administration), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 hours post-meal. These values will be used for PPG analyses with the goal of deriving reduction in the maximum glucose exposure in the 4-hour period after the breakfast meal following Soliqua 100/33 administration at Week 16 compared with baseline. During both baseline and end-of-treatment assessments, removal of the CGM device and download of data will be done after completion of the MMTT (Section 13.1).

The MMTT includes a standardized meal (ie, Boost Very High Calorie) that contains approximately 530 kcal and is composed of 19% carbohydrates, 44% protein, and 33% fat. The composition and the quantity of the standardized meal must be identical throughout the study period.

During the baseline period (ie, Visit 3.1), on the day of the MMTT, the participants 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). At the end of the treatment period (ie, Visit 7), the MMTT will also be performed in a fasted state (eg, no consumption of any food or drink for at least 8 hours, except water, before the scheduled meal test), and participants will receive their Soliqua 100/33 dose at the study site 30 minutes before the start of the test (ie, consumption of the meal and just after the first blood draw).

For participants who discontinue study treatment prematurely, the visit window can be extended by 14 days to collect the CGM data, followed by the MMTT data, before they permanently discontinue the treatment.

6.2.3 Fasting SMPG

Participants will be supplied with a glucometer kit and an eDiary at the screening visit. Appropriate training will be provided to the participants related to proper use of the glucometer and eDiary completion. Fasting SMPG values (lowest values in conjunction with measurements from the previous 3 days) will be used to titrate and adjust Soliqua 100/33 doses and monitor glycemic control. Sound clinical judgment should be exercised during titration to further up-titrate if the lowest value from the last 3 measurements is between 80 to 100 mg/dL but the 2 other values are above 100 mg/dL and further titration is required to manage hyperglycemia. The participants are required to measure fasting SMPG values before breakfast at least 3 to 4 times per week throughout the study period (to inform each dose adjustment) and record the results in the eDiary. During the titration period, fasting SMPG should be performed on each of the 3 to 4 days before each dose adjustment. (Note: Additional titration is at the discretion of the investigator with the goal of achieving glycemic targets while minimizing the risk of hypoglycemia and hyperglycemia.)

6.2.3.1 SMPG During Symptomatic Hypoglycemia

Whenever participants experience hypoglycemia symptoms, they (or others, if applicable) should measure plasma glucose, if possible. Participants should be instructed to measure plasma glucose levels before carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate carbohydrate/glucose rescue before confirmation with the SMPG values. Participants must contact the investigator as soon as possible following hypoglycemia events for review and so

that a decision regarding any necessary actions can be made. Participants should be instructed to measure plasma glucose levels again after the event resolves.

6.2.4 FPG Measurements

Blood samples will be collected to determine FPG at the time points specified in the SoE (Section 13.1) and will be measured at a central laboratory. For the scheduled site visits, participants are required to arrive fasting without administering the Soliqua 100/33 injection. Fasting is defined as no food intake in the 8 hours before blood sampling, except water.

6.2.5 HbA1c Measurements

Blood samples will be collected to measure HbA1c during the screening and run-in periods and at Visit 3.1 (before administration of the meal) at the central laboratory, to determine study eligibility and at the end of the 16-week treatment period (Visit 7), to determine change in glycemic control.

6.2.6 Assessment of Patient-Reported Outcome

Diabetes Medication Satisfaction Tool

The assessment of treatment-related impact on participants' health-related quality of life (HRQoL) and their satisfaction with diabetes therapy will be assessed using the DM-SAT questionnaire (Anderson et al 2009) at the baseline visit before stopping or down-titration of baseline therapies and at the end of the treatment period (Section 13.1). The DM-SAT questionnaire (Section 13.2) is a 16-item measure with 4 subscales assessing wellbeing (3 items), medical control (3 items), lifestyle (5 items), and convenience (5 items).

Participants will be requested to complete the DM-SAT questionnaire by themselves, independently from the investigator or site staff, and without any help from friends or relatives. For validity purposes, the questionnaire should be completed by participants in a quiet place, at the start of the visit before any other study tests or procedures are performed or Soliqua 100/33 is administered.

6.3 Safety Assessments

6.3.1 Physical Examination

A complete physical examination (including body weight) will be performed, per standard of care, in order to assess the health status of the participants at time points described in the SoE (Section 13.1). Height measurements in conjunction with body weight will be utilized to calculate BMI during the screening period.

Body weight will be measured to allow the estimation of change from baseline to Week 16. While measuring body weight the participant should be wearing only undergarments or very light clothing and no shoes and have an empty bladder.

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

The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at zero and the balance bar aligned. The participant should stand in the center of the platform as standing off-center may affect the measurement. The weights are moved until the beam balances (the arrows are aligned). The weight should be read and recorded in the eCRF and source documents.

Self-reported weights are not acceptable on physical examination; participants must not read the scales themselves.

6.3.2 Hypoglycemia Events

During the study, participants must be instructed to document any hypoglycemia events in their eDiary. Hypoglycemia will be reported in the specific hypoglycemia event information form in the eCRF with onset date and time; symptoms and/or signs; the SMPG value, if available; and the treatment. A hypoglycemia event that fulfills the seriousness criteria will also be documented on the SAE form in the eCRF.

Hypoglycemia will be evaluated in accordance with the consensus report of a steering committee on levels of hypoglycemia (Agiostratidou et al 2017). These levels are consistent with ADA standard of care 2021 recommendations (ADA 2021a).

The following are the categories of interest:

- Overall hypoglycemia.
- Confirmed hypoglycemia.
    - ADA Level 1: A measurable glucose concentration of <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) that can alert a person to take action. Blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a marker of physiological hypoglycemia in humans. Recurrent episodes of hypoglycemia lead to increased hypoglycemia unawareness, Therefore, glucose levels <70 mg/dL (3.9 mmol/L) are clinically important, independent of the severity of acute symptoms.
    - ADA Level 2: A measurable glucose concentration of <54 mg/dL (3.0 mmol/L) that needs immediate action. At approximately 54 mg/dL (3.0 mmol/L), neurogenic and neuroglycopenic hypoglycemia symptoms begin to occur, ultimately leading to brain dysfunction at levels <50 mg/dL (2.8 mmol/L). Neuroglycopenic symptoms, including behavioral changes, visual changes, seizure, and loss of consciousness, are the result of central nervous system neuronal glucose deprivation.
    - ADA Level 3: A severe event characterized by altered mental and/or physical functioning that requires assistance* from another person for recovery. Severe hypoglycemia captures events during which the symptoms associated with hypoglycemia affect a patient such that the patient requires assistance from others.

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

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

6.3.3 Clinical Safety Laboratory Assessments

All clinical safety laboratory assessments will be performed by a central laboratory. The list of clinical laboratory tests to be performed is provided in Section 13.4. The timing and

frequency of sample collections are provided in the SoE (Section 13.1). Additional tests may be performed at a local or central laboratory at any time during the study as determined necessary by the investigator or required by local regulations. If they are used to evaluate an AE (diagnostic, follow-up, outcome), the results must be entered into the eCRF (Section 13.4).

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.
- The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings associated with the underlying disease or vital signs will **not** be considered clinically significant or be reported as AEs **unless** one of the following criteria is met:
    - Participant is symptomatic (and/or laboratory values are or vital signs are clinically significant per the investigator's discretion).
    - Participant requires either corrective treatment or consultation.
    - Participant requires Soliqua 100/33 treatment to be discontinued or modification of dosing.
    - Event fulfills a seriousness criterion.
    - Event meets the definition of an AESI (Section 6.3.5.2).
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal/baseline or are no longer considered clinically significant by the investigator.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 13.4, must be conducted in accordance with the laboratory manual and the SoE (Section 13.1).
- The recommended decision tree for the management of ALT increase is provided in Appendix 13.6.

6.3.4 Vital Signs

Vital signs (heart rate, systolic blood pressure [BP], and diastolic BP) will be recorded at the time points specified in the SoE (Section 13.1).

- Blood pressure will be assessed in a seated position using the same device (automated BP monitor or a manual sphygmomanometer) for each participant.
- Seated BP should be measured in both arms after at least a 5-minute rest, and then again after 1 minute in both arms while the participant is in a seated position. The arm with the highest systolic BP will be determined at this visit, and the BP should be measured using this arm throughout the study. This highest value will be recorded in the eCRF.
- At subsequent visits, BP should be measured using the participant's designated arm, to be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).
- Heart rate will be measured concurrently with the measurement of seated BP.
- Vital sign abnormalities are to be recorded as AEs only if at least one of the following criteria is met:
    - Participant is symptomatic (and/or vital signs are clinically significant per the investigator's discretion).
    - Participant requires either corrective treatment or consultation.
    - Participant requires Soliqua 100/33 treatment to be discontinued or the dose to be modified.
    - Event fulfills a seriousness criterion.
    - Event meets the definition of an AESI (Section 6.3.5.2).

6.3.5 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. The investigator remains responsible for following up on all AEs that are serious, considered

related to the study treatment or study procedures, or caused the participant to discontinue Soliqua 100/33 treatment and/or the study.

All AEs (serious or nonserious) will be collected from the signing of the ICF until the follow-up visit (Section 13.1).

The definitions of AEs and SAEs are provided in Section 13.5. The definition of an AESI is provided in Section 6.3.5.2.

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this be longer than 24 hours of awareness, as indicated in Section 6.3.5.5. The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

After the initial AEs/AESIs/SAEs report, the investigator is required to proactively follow-up with each participant at subsequent visits/contacts. At the prespecified study end date, all SAEs and AESIs (as defined in Section 6.3.5.2), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 4.4.2). Further information on follow-up procedures is provided in Section 13.5.3.

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

6.3.5.1 Suspected Unexpected Adverse Events

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

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

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

6.3.5.2 Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

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

- Pregnancy of a female participant enrolled in the study as well as pregnancy occurring in a female partner of a male participant enrolled in the study with IMP/NIMP.
    - Pregnancy will qualify as an SAE only if it fulfills one of the seriousness criteria (Section 13.5.2).
    - If it is a pregnancy in a female participant, IMP should be discontinued.
    - Follow-up of the pregnancy of a female participant or a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or nonserious) with IMP/NIMP.
    - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the investigator or spontaneously reported by the participant and is defined as any dose administration that, in the investigator's opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin or is at least twice the intended dose within the intended therapeutic interval (for example, for a participant prescribed 60 units/20 µg of Soliqua 100/33 once a day, administration of ≥120 units of insulin glargine and ≥40 µg of lixisenatide once a day would be considered an overdose), adjusted according to the tested drug.

- Asymptomatic overdose has to be reported as a standard overdose. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim, and symptoms, if any, must be entered on separate AE/SAE forms.

- Increase in ALT (>3 × ULN; Section 13.6).

6.3.5.3 Pregnancy

A urine pregnancy test will be performed at time points specified in the SoE (Section 13.1). To ensure participant safety, each pregnancy must be reported to Sanofi within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of mother and child, even if the participant was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

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

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

6.3.5.4 Eliciting and Documenting AEs

Adverse events will be assessed from the time the participant signs the ICF until exit from the study.

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

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

In addition to participant's observations, AEs identified from any study data (eg, laboratory values, physical examination findings) or identified from review of other documents

(eg, participant's eDiary) that are relevant to participant's safety will be documented on the AE page in the eCRF.

6.3.5.5 Reporting AEs

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

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that meets criteria of an SAE (Section 13.5.2) or an AESI (Section 6.3.5.2) must be reported to **PPD Pharmacovigilance** immediately (ie, within 24 hours) after site personnel first learn about the event (Section 13.5.4).

6.3.5.6 Assessment of Severity

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

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

6.3.5.7 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process (Section 13.5.3), but it is not a factor in determining what is or is not

reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

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

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

6.3.5.8 Follow-up of Participants Reporting AEs

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

6.3.6 Safety Monitoring Committee

An independent safety monitoring committee will not be formed for this study. The medical monitor and sponsor will hold monthly reviews of all AEs.

6.3.7 Guidelines for Reporting Product Complaints

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

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

6.4 Outcomes Research Assessments

The assessment of treatment-related impact on participants' HRQoL and their satisfaction with diabetes therapy will be assessed using the DM-SAT questionnaire, as described in Section 6.2.6.

6.5 Sample Collections

Site personnel will collect blood samples at the visits specified in the SoE (Section 13.1). These samples will be processed at the site and shipped the same day to a central laboratory, as specified in the laboratory manual. The central laboratory will analyze blood samples for PPG measures, HbA1c, and FPG, clinical chemistry, hematology, and biomarkers of β-cell function (during the MMTT). Results will be returned to the site within 48-72 hours.

6.6 Use of Biological Samples And Data For Future Research

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

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related to the drug, the mechanism of action, the disease, or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins, or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease, or its associated conditions.

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

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

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

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of the retention period will be destroyed. If a participant requests destruction of their samples before the end of the retention period, the investigator must notify the sponsor in writing. In such cases, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

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

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

6.6.1 Assessment of β-Cell Function Indices

β-cell function biomarkers (plasma glucose, C-peptide, and insulin) will be collected from all eligible participants at baseline during the MMTT for assessment of β-cell responsivity, insulin and glucose sensitivity, and any relationships to glycemic control. After database lock, data will be transferred to an academic partner who will utilize modelling techniques to derive these measures. These results will be reported separately.

7 Study-Specific Committees

No scientific steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

8 Statistical Considerations

8.1 Estimands and Intercurrent Events

The estimand framework is provided in Table 8-1.

Table 8-1 Estimand Framework

Estimand Definition	Variable (or Endpoint)	Strategy for Addressing Intercurrent Event	Population-Level Summary
Estimand [Primary]			
The primary estimand is the mean change in the percentage of TIR (70-180 mg/dL) from baseline to Week 16. The primary estimand will be estimated based on the efficacy analysis set using obtained measurements, regardless of intercurrent events.	Mean change in percentage of TIR at Week 16 from baseline	Treatment policy strategy	Mean and 95% CI of change in percentage of TIR at Week 16 from baseline
Estimand [Key Secondary]			
Mean percent changes of CV at Week 16 from baseline among the efficacy analysis set, regardless of intercurrent events	Mean percent changes of CV at Week 16 from baseline	Treatment policy approach	Mean and 95% CI
Mean mg/dL change of mean daily blood glucose at Week 16 from baseline among the efficacy analysis set, regardless of intercurrent events	Mean mg/dL change of mean daily blood glucose at Week 16 from baseline	Treatment policy approach	Mean and 95% CI
Mean mg/dL change in the maximum PPG exposure in the 4-hour period after the breakfast meal at Week 16 from baseline among the efficacy analysis set, regardless of intercurrent events	Mean mg/dL change in maximum PPG exposure in the 4-hour period after the breakfast meal at Week 16 from baseline	Treatment policy approach	Mean and 95% CI

Estimand Definition	Variable (or Endpoint)	Strategy for Addressing Intercurrent Event	Population-Level Summary
Mean percent change in TAR >180 mg/dL at Week 16 from baseline among the efficacy analysis set, regardless of intercurrent events	Mean percent change in TAR >180 mg/dL at Week 16 from baseline	Treatment policy approach	Mean and 95% CI

Abbreviations: CI, confidence interval; CV, coefficient of variation; PPG, postprandial glucose; TAR, time above range; TIR, time in range.

The following intercurrent events for the primary estimand will be handled by the treatment policy strategy: initiation of rescue medication other than the study IMP, discontinuation of IMP, withdrawal from the study, and recording of <80% of evaluable CGM data per 24-hour period over 10 days of a 14-day period, during the run-in period as well as the end of the treatment period (ie, from Weeks 14 to 16; Section 13.9). This estimand aims to reflect the estimated treatment effect under the intention-to-treat (ITT).

8.2 Statistical Hypothesis

The null hypothesis (H0) for the primary endpoint is that the efficacy analysis set will have no improvement in TIR at Week 16 compared with baseline. The alternative statistical hypothesis is that the efficacy analysis set will have an increased TIR at Week 16 compared with baseline at the significance level of 0.05.

8.3 Sample Size Determination

A total of 100 participants will be enrolled in the study. Sufficient participants will be screened from approximately 15 sites to include 100 patients, such that approximately 82 evaluable participants complete the study (anticipating that approximately 15% of participants discontinue the study before Week 16).

The sample size is based on the primary objective to demonstrate the significant mean change (ie, increase) in the percentage of TIR (70-180 mg/dL) from baseline to Week 16 with sufficient power. A sample size of 82 participants will have 95% power to detect an absolute increase in TIR means of 10%, assuming a standard deviation (SD) of 25 for the change in TIR, with a two-sided type I error of 0.05. Anticipating a 15% loss to follow-up rate, 100 participants would need to be enrolled.

Assumptions for Sample Size Determinations

- Patients with an HbA1c ≥9% are in range 40% of the time or less (Batellino et al 2019).
- Per Vigersky and McMahon, every 10% increase in TIR corresponds to 0.8% HbA1c reduction (Vigersky and McMahon 2019).
- Post hoc analyses from the LixiLan-O study in patients with an HbA1c of ≥9% produced an HbA1c reduction of 2.9% at 30 weeks (Davies et al 2019). Therefore, 0.8% HbA1c reduction (considered equal to 16% improvement in TIR) at Week 16 seems reasonable.
- Assumption for SD is 25. In the AWARD-4 study in patients with T2DM, the increase in TIR at Week 26 was 20% to 30%, and the SE was approximately 3.0 (corresponding to an SD of approximately 20) (Jendle et al 2016).

8.4 Analysis Sets

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

- Enrolled set: All eligible participants who are dispensed Soliqua 100/33 and sign the ICF.
- Efficacy analysis set: All enrolled participants who receive ≥1 dose of Soliqua 100/33 and have evaluable CGM data at baseline.
- Safety set: All enrolled participants who receive ≥1 dose of Soliqua 100/33.

8.5 Description of Subgroups to Be Analyzed

The following subgroups are planned for the primary analyses, if the number of participants in each subgroup is sufficient: participants with OAD only or OAD plus GLP-1 RA at baseline. The number of patients deemed sufficient for a subgroup analysis will be determined in the statistical analysis plan (SAP).

8.6 Accountability, Demographics, and Baseline Characteristics

Treatment adherence, demographics, and baseline characteristics will be summarized in descriptive tables. Continuous data will be summarized using number of observations

available, mean, SD, quartile ranges, minimum, median, and maximum. Categorical data will be summarized using count and percentage.

8.6.1 Adherence

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

$$\text{Adherence rate (\%)} = \left[\frac{\text{Total number of days with Soliqua 100/33 injection}}{\text{Planned number of days with Soliqua 100/33 injection}} \right] \times 100$$

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

Treatment adherence will be summarized using mean, SD, median, and range for the safety set. In addition, the percentage of participants who have <60%, ≥60% to <80%, ≥80% to ≤100%, and >100% adherence will be summarized.

The duration of IMP exposure will be calculated as date of the last IMP injection – date of the first IMP injection + 1.

8.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS Enterprise software Version 7.1 or higher. 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 participants having non-missing assessments at a specific visit). The baseline value is defined as the last available value before the first injection of Soliqua 100/33. All efficacy analyses (primary, key secondary, secondary, and other efficacy endpoints) will be performed on the efficacy analysis set. Analysis of demographics, baseline characteristics, and prior and concomitant medications will be provided in detail in the SAP. The extent of study treatment exposure and adherence will be assessed and summarized with dose frequency and duration of treatment.

Continuous data will be summarized using number of observations available, mean, SD, minimum, median, and maximum. Categorical data will be summarized using count and percentage.

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

All statistical tests will be 2-sided and performed using a 0.05 significance level, leading to 95% (2-sided) confidence intervals (CIs).

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

8.7.1 Overview of Statistical Methods: Estimation of Estimands and Sensitivity Analyses

A summary of statistical methods, including sensitivity analyses, is provided in Table 8-2.

Table 8-2 Summary of Statistical Methods, Including Sensitivity Analyses

Main Estimation					
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 1a (Primary)	Mean change in the percentage of TIR (70-180 mg/dL) from baseline to Week 16 among the entire study population. The primary estimand will be estimated based on the efficacy analysis set using obtained measurements. The value for the mean change in the percentage of TIR will be used regardless of intercurrent events at Week 16.	Efficacy analysis set	Missing endpoint at Week 16 due to technical issues with the CGM device will be excluded from the analysis. Missing endpoint at Week 16 due to other reasons than technical issues will be imputed by the baseline value.	Mean and its associated 95% CI will be calculated on an overall efficacy analysis set. A one-sample t-test will be applied to test the significance of changes at Week 16 over baseline.	The sensitivity analysis for the primary outcome will be conducted with all missing data imputed using BOCF approach. In case there is substantial missing CGM data, a second sensitivity analysis may be conducted on participants with evaluable data to estimate the primary endpoint at Week 16. Mean and its associated 95% CI will be reported.

Abbreviations: BOCF, baseline observation carry forward; CI, confidence interval; CGM, continuous glucose monitoring; TIR, time in range.

8.7.2 Analysis of Primary Endpoint

8.7.2.1 Main Estimation of Primary Estimand

The primary endpoint is to demonstrate the improvement from baseline in the percentage of TIR of 70 to 180 mg/dL during the last 2 weeks of treatment (Weeks 15 and 16) for the entire study population. The percentage of time spent in the glycemic target range will be calculated as 100 times the number of recorded measurements in the glycemic target range, (70-180 mg/dL) inclusive, divided by the total number of recorded measurements.

As described in Table 8-2, the mean and its associated 95% CI will be used to describe the changes in TIR (70-180 mg/dL) at Week 16 from baseline. A one-sample t-test will be applied to test the significance of changes. A p-value <0.05 will be considered significant.

As part of the definition for the efficacy analysis set, evaluable data (ie, not missing) is defined as the availability of at least 10 out of 14 days (not necessarily consecutive) with at least ≥80% of evaluable CGM data per 24-hour period during the run-in period as well as the end of the treatment period (ie, from Weeks 14 to 16; Section 13.9), otherwise it will be considered as missing.

The primary estimand will be estimated based on the efficacy analysis set using obtained measurements, regardless of intercurrent events. Table 8-2 provides more details regarding the missing data definition.

The missing data related to the primary estimand due to lost-to-follow-up or treatment discontinuation will be imputed with their baseline observation carry forward (BOCF). Missing data due to technical issues of CGM devices will not be imputed. Details of handling missing data are provided in Section 8.7.3.3.

8.7.2.2 Sensitivity Analysis of Primary Endpoint

Sensitivity analysis for the primary outcome will be conducted by imputing all missing data (regardless of reasons) with BOCF.

If there is substantial missing CGM data from for the primary outcome, an additional sensitivity analysis will be conducted on participants with evaluable data to estimate the

primary endpoint at Week 16 (data from participants who discontinue their treatment before Week 16 will also be included as long as they have evaluable CGM data). Mean and its associated 95% CI will be reported.

8.7.2.3 Supplementary Analysis of Primary Endpoint

Analysis of the primary endpoint will be summarized by baseline subgroups (ie, OAD only or OAD plus GLP-1 RA).

8.7.3 Analysis of Key Secondary Efficacy Endpoints

8.7.3.1 Main Estimation of Key Secondary Estimand

Change in Glycemic Control and Variability

Mean changes for continuous outcomes (eg, CV, mean daily blood glucose, maximum PPG exposure in the 4 hours after the breakfast meal, TAR >180 mg/dL) will be presented at baseline and at the end of the treatment period (Week 16). Mean (SD) and associated 95% CI, as well as minimum, median, and maximum will be provided.

The key secondary estimand will be estimated based on the efficacy analysis set using measurements obtained during the study, regardless of intercurrent events. Missing data related to the key secondary estimand will be imputed with their BOCF. Similarly to analysis of primary estimand, missing data due to technical issues of CGM devices will not be imputed.

8.7.3.2 Sensitivity Analysis of Key Secondary Endpoints

No sensitivity analysis is planned for key secondary endpoints.

8.7.3.3 Handling of Missing Data

Missing data will be handled differently in accordance with the reasons for the missing data for both primary and key secondary endpoints. If the missing data are due to technical issues with the CGM device (ie, CGM data are not evaluable if at least 10 out of 14 days [not necessarily consecutive] have <80% of evaluable CGM data per 24-hour period during the run-in period as well as the end of the treatment period [ie, from Weeks 14

to 16]), the participant will be excluded from the analysis (missing completely at random [MCAR] approach). For other reasons for missing measurements (eg, lost to follow-up, discontinued treatment), the Week 16 assessment will be imputed with the baseline value carried forward (missing not at random [MNAR], conservative approach). The assumption that data are MCAR will be evaluated using an association test (eg, Chi-square test for categorical covariates and Pearson correlation coefficient or two-sample t-test for continuous covariates) between baseline covariates and missing data status (ie., participants who have missing data for primary endpoint versus those who have complete data). The reasons for missing the primary endpoint at Week 16 (eg, lost to follow-up, discontinued treatment) will also be presented.

Multiple Comparisons and Multiplicity

A hierarchical testing procedure will be performed. Key secondary endpoints will be evaluated with a one-sample t-test to determine whether there is any change at Week 16 over baseline in succession in accordance with the hierarchy and as long as the endpoints continue to show statistical significance. If one test is nonsignificant ($p > 0.05$), then the testing will be stopped (or consider all further tests to be only secondary, and no formal conclusions can be drawn).

8.7.4 Analyses of Secondary Endpoints

Mean changes for continuous outcomes (eg, other measures of glycemic control and variability: TIR [70-180 mg/dL] for four 6-hour time segments, Glucose Management Indicator [GMI] <7% and <9%, 4-hour PPG area under the concentration versus time curve from 0 to 4 hours (AUC_{0-4h}) after start of the breakfast meal, and time to maximal PPG concentration) will be presented at baseline and at the end of the treatment period (Week 16). Mean (SD) and associated 95% CI, as well as minimum, median, and maximum will be provided.

Binary outcomes (eg, change in the proportion of patients achieving CV <36% at Week 16, the proportion of patients at Week 16 who spend <15 minutes/day at a glucose level <54 mg/dL) will be summarized with proportions and 95% CI using the Clopper Pearson exact method.

8.7.5 Analyses of Other Efficacy Endpoints

Mean changes for continuous outcomes (eg, additional measures of glycemic control and variability: mean of daily difference [MODD] of glucose levels, TAR >250 mg/dL, TBR <70 mg/dL, and HbA1c %) will be presented at baseline and at the end of the treatment period (Week 16). Mean (SD) and associated 95% CI, as well as minimum, median, and maximum will be provided.

The correlation of TIR to patient-reported outcome (PRO), HbA1c, and relationship of patients requiring 60 units/day of insulin glargine (related to TIR >70%) at Week 16 will be assessed using Pearson correlation coefficient.

8.7.6 Assessment of β-Cell Function Indices

β-cell function biomarkers (plasma glucose, C-peptide, and insulin) collected at baseline will be analyzed utilizing minimal modelling by an external academic partner for all eligible participants to determine β-cell responsivity, insulin and glucose sensitivity, and any relationships to glycemic control. The β-cell function indices will be included as a post hoc analyses and reported separately.

8.7.7 Analysis of PRO Endpoint

Change in diabetes medication treatment-related impact and satisfaction, as measured by the DM-SAT, from baseline to Week 16 will be analyzed using the efficacy analysis set and described as mean (SD) and associated 95% CI, as well as minimum, median, and maximum for overall score and by subscales.

8.7.8 Safety Analyses

All safety and tolerability endpoints will be described by number, proportion, and the associated 95% CI for proportions. Adverse event incidence tables will be presented by system organ class (SOC; sorted by internationally agreed order), high-level group term (HLGT), high-level term (HLT), and preferred term (PT) sorted in alphabetical order with the number (n) and percentage of participants experiencing an AE. Participants with more than 1 AE will be counted only once. The denominator for computation of percentages will be the safety set.

8.7.8.1 Adverse Events

A treatment-emergent AE is an event that has onset date (or increase in severity) during the on-treatment observation period.

The most frequent AEs will be defined as PTs that are experienced by at least 5% of the participants in any of the treatment arms.

All AEs will be coded using the most recent version of the MedDRA in-use by the sponsor at the time of database lock.

8.7.8.2 Hypoglycemia Events

Hypoglycemia events will be summarized similarly to the treatment-emergent AEs for on-treatment observation periods based on the safety set. In addition, hypoglycemia events will be counted with multiple episodes per participant, if available, and the event rate per person-years will be reported overall and by level.

8.8 Data Quality Assurance

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

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

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

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

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

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

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

8.8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include a participant's eDiary, laboratory reports (Section 13.8).

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

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

Investigative site personnel will enter participant data into Medidata Rave. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data, CGM device, PRO).

Clinical data management will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events and concomitant medication terms will be coded using MedDRA and WHODrug, respectively. After database lock, each study site will receive their site-specific eCRF data as entered into Medidata Rave for the study,

including full discrepancy and audit history. Additionally, a copy of all data from the study will be created and sent to the sponsor for storage. In all cases, participant initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Institutional Review Board

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Participant Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB

submission. Once reviewed, the consent will be submitted by the investigator to their IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participants must sign the revised form.

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

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

10 Investigator's Obligations

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

10.1 Confidentiality

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

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

10.2 Data Protection

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

When archiving or processing personal data pertaining to the investigator and/or to the participants, the sponsor takes all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

Protection of Participant Data

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

This CGM study will attempt to represent a diverse set of US people with T2DM as advised by the FDA. These people represent a growing proportion of the US population, are historically under-represented in clinical studies, and are disproportionately affected by T2DM. For example, non-Hispanic Black, Hispanic, and American Indian/Alaska native adults are twice as likely to have diagnosed diabetes as non-Hispanic White adults.

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information that would make the participant identifiable will not be transferred to the sponsor.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the following steps necessary for the development of the investigational product, including to support negotiations with payers and the publication of results.

Protection of Data Related to Professionals Involved in the Study

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

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

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

- Personal data can be communicated to the following recipients:

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

- Personal data may be transferred to entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law, including the following:

    - The standard contractual clauses of the European Commission for transfers to our partners and service providers.
    - Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals are able to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL), or any competent local regulatory authority.

- Personal data of professionals will be retained by Sanofi for up to 30 years, unless further retention is required by applicable regulations.

- In order to facilitate the maintenance of investigators' personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows investigators to keep their data up-to-date once, for access by all pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.

- Professionals have the right to request access to and rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.3 Financial Disclosure and Obligations

Investigators and sub-investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

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

10.4 Investigator Documentation

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

- IRB approval.
- Original investigator-signed agreement page of the protocol.
- Curriculum vitae for the investigator and each sub-investigator.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the participant.
- Signed Clinical Study Agreement.

10.5 Study Conduct

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

10.6 Adverse Events and Study Report Requirements

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

10.7 Investigator's Final Report

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

11 Study Management

11.1 Monitoring

11.1.1 External Data Monitoring Committee

No data monitoring committee is planned for this study.

11.1.2 Monitoring of the Study

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

The medical monitor and sponsor will hold monthly meetings to review AEs noted during the month, unless an SAE is noted and reported as described in Section 6.3.5.5.

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

11.1.3 Inspection of Records

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

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

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

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

11.2.2 Protocol Deviations

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

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the participant or investigator that results in a significant additional risk to the participant. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the participant without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines and will lead to the participant being withdrawn from the study (Section 4.4).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although Sanofi has every intention of completing the study, Sanofi reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date of the last visit of the last participant in the study.

11.4 Final Report

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

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

Upon completion of the CSR, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate. The study results will be posted on publicly available clinical study registers.

11.5 Records Retention

Essential documents should be retained for 25 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 25 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution as to when these documents no longer need to be retained.

11.6 Publication Policy, Disclosure, and Clinical Study Registration

11.6.1 Publication Policy and Disclosure

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement between the sponsor and the investigator and in line with International Committee of Medical Journal Editors authorship requirements.

11.6.2 Clinical Study Registration

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

11.6.3 Clinical Study Results Disclosure

Study Participants

Sanofi shares information about clinical studies and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical study disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, European Union (EU) clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

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

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

Professionals Involved in the Study or in the Drug Development Program

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

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13 Appendices

13.1 Appendix: Schedule of Events

Table 13-1 Schedule of Events

Study Period	Screening	Run-in	Treatment[a]							Follow-up
			Baseline	Titration[b]						
Visit[c]	**1**	**2**	**3.1[d]**	**3.2[e,f]**	**4.0–4.6[g]**	**5**	**5.1–5.4[h]**	**6**	**7[i]**	**Unscheduled[j]**	**8**
Visit Type	**Clinic**	**Clinic or Home**	**Clinic**	**Phone[e]**	**Phone**	**Clinic or Home**	**Phone**	**Clinic or Home**	**Clinic**	**Clinic or Home**	**Phone**
Week	**–4**	**–2**	**0**	**0**	**1 to 7**	**8**	**9 to 12**	**14**	**16**		**18**
Day	**–28**	**–15[k]**	**–1**	**0**	**1 to 49**	**56**	**63 to 84**	**98**	**112**		**126**
Window (Days)				**7(±2)[e]**		**±3**		**±3**	**±3**		**±3**
Informed consent	X										
Inclusion and exclusion criteria	X		X								
Demography (including height and body weight)	X										
Medical/surgical history	X										
Current medications	X										
Physical examination	X								X		
Body weight and height[l]	X		X						X		
Dispense glucometer	X										
Fasting SMPG[m]		<----------X---------->									

Study Period	Screening	Run-in	Treatment[a]							Follow-up
			Baseline	Titration[b]						
Visit[c]	**1**	**2**	**3.1[d]**	**3.2[e,f]**	**4.0–4.6[g]**	**5**	**5.1–5.4[h]**	**6**	**7[i]**	**Unscheduled[j]**	**8**
Visit Type	**Clinic**	**Clinic or Home**	**Clinic**	**Phone[e]**	**Phone**	**Clinic or Home**	**Phone**	**Clinic or Home**	**Clinic**	**Clinic or Home**	**Phone**
Week	**–4**	**–2**	**0**	**0**	**1 to 7**	**8**	**9 to 12**	**14**	**16**		**18**
Day	**–28**	**–15[k]**	**–1**	**0**	**1 to 49**	**56**	**63 to 84**	**98**	**112**		**126**
Window (Days)				**7(±2)[e]**		**±3**		**±3**	**±3**		**±3**
HbA1c measurement[n]	X	X	X						X		
Blinded CGM device application[o]		X						X			
MMTT[p]			X						X		
CGM device removal and data download (after the MMTT)[q]			X						X		
CGM compliance assessment[r]			X						X		
MMTT-derived β-cell function (insulin, C-peptide, and plasma glucose)[s]			X						X		
MMTT PPG measures[s]									X		

Study Period	Screening	Run-in	Treatment[a]							Follow-up
			Baseline	Titration[b]						
Visit[c]	**1**	**2**	**3.1[d]**	**3.2[e,f]**	**4.0–4.6[g]**	**5**	**5.1–5.4[h]**	**6**	**7[i]**	**Unscheduled[j]**	**8**
Visit Type	**Clinic**	**Clinic or Home**	**Clinic**	**Phone[e]**	**Phone**	**Clinic or Home**	**Phone**	**Clinic or Home**	**Clinic**	**Clinic or Home**	**Phone**
Week	**–4**	**–2**	**0**	**0**	**1 to 7**	**8**	**9 to 12**	**14**	**16**		**18**
Day	**–28**	**–15[k]**	**–1**	**0**	**1 to 49**	**56**	**63 to 84**	**98**	**112**		**126**
Window (Days)				**7(±2)[e]**		**±3**		**±3**	**±3**		**±3**
Last doses of daily DPP-4i and daily GLP-1 RA (on the morning of Day – 1, the day before the first dose of Soliqua 100/33) and down-titration of SU dose to 50% (when starting Soliqua 100/33)[t]			X	X							
Dispense IMP			X			X				X	
Soliqua pen instruction[u]			X	X							
eDiary set-up	X										
eDiary completion	<----------X---------->										
Daily IMP dosing[t]				<----------X---------->							
IMP dose adjustments					X	X	X			X	
Concomitant medications			X	X	X	X	X	X	X	X	X
IMP adherence assessment						X		X	X		
FPG[v]			X					-	X		
DM-SAT[w]			X					-	X		

Study Period	Screening	Run-in	Treatment[a]							Follow-up
			Baseline	Titration[b]						
Visit[c]	**1**	**2**	**3.1[d]**	**3.2[e,f]**	**4.0–4.6[g]**	**5**	**5.1–5.4[h]**	**6**	**7[i]**	**Unscheduled[j]**	**8**
Visit Type	**Clinic**	**Clinic or Home**	**Clinic**	**Phone[e]**	**Phone**	**Clinic or Home**	**Phone**	**Clinic or Home**	**Clinic**	**Clinic or Home**	**Phone**
Week	**–4**	**–2**	**0**	**0**	**1 to 7**	**8**	**9 to 12**	**14**	**16**		**18**
Day	**–28**	**–15[k]**	**–1**	**0**	**1 to 49**	**56**	**63 to 84**	**98**	**112**		**126**
Window (Days)				**7(±2)[e]**		**±3**		**±3**	**±3**		**±3**
Hypoglycemia events[x]	X	X	X	X	X	X	X	X	X	X	X
Recording of AEs/SAEs (including AESIs)	X	X	X	X	X	X	X	X	X	X	X
Product complaints					X	X	X	X	X		
Vital signs (including heart rate, systolic and diastolic BP)	X		X						X		
Calcitonin	X										
Clinical chemistry	X		X						X		
Hematology	X		X						X		
Urinalysis[y]	X		X						X		
Pregnancy test[z]	X		X			X			X		

Abbreviations: ADA, American Diabetes Association; AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; BP, blood pressure; CGM, continuous glucose monitoring; DM-SAT, Diabetes Medications Satisfaction Questionnaire; DPP-4i, dipeptidyl peptidase-4 inhibitor; DTP, direct-to-patient; eDiary, electronic diary; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; Hb, hemoglobin; HbA1c, glycated hemoglobin; HCP, healthcare provider; IMP, investigational medicinal product; MMTT, mixed-meal tolerance test; OAD, oral antidiabetic drug; PPG, postprandial glucose; SAE, serious adverse event; SMPG, self-measured plasma glucose; SU, sulfonylurea.

[a] For participants who discontinue study treatment prematurely, the visit window can be extended by 14 days to collect the CGM data, followed by MMTT data, before they permanently discontinue the treatment. Before permanent discontinuation of treatment regardless of the reason or as soon as possible after the decision for discontinuation has been made, if possible, the participant will undergo all procedures planned for the last dosing day with Soliqua 100/33 and the follow-up visit (ie, Visit 7 and above).

[b] During the titration period, the dose of IMP will be adjusted upwards or downwards by 2 to 4 units every week, or at the investigator's discretion, based on the participant's blood glucose monitoring results, with the objective of safely attaining a fasting SMPG value of 80 to 100 mg/dL, as well as other glycemic goals,

while minimizing the risk of hypoglycemia and hyperglycemia. The duration of the titration period and number of phone contacts to safely meet the study goals will also be at the discretion of the investigator.

[c] Participants will have the choice to have Visits 2, 5, and 6 performed at the study site or at home. This choice is to be determined at the screening visit. Participants who opt for site visits should be encouraged not to change to home visits during the study period. However, if this is unavoidable, the home health provider and the sponsor-approved courier company for IMP shipment will need at least 72 hours' notice from the investigator to arrange a home visit and DTP IMP supply, if required.

[d] Participants on weekly GLP-1 RA should administer their last dose 7 (± 2) days before the first dose of Soliqua 100/33, whereas the last dose of daily DPP-4i and daily GLP-1 RA (oral or injectable) should be administered on the morning of Day –1, the day before the first dose of Soliqua 100/33.

[e] It is the first day of Soliqua 100/33 administration and includes a phone contact to ALL participants to ensure that all administration procedures were successfully executed and to answer any questions. The first day of Soliqua 100/33 administration (ie, Visit 3.2, Day 0) for participants on weekly GLP-1 RA will depend on their administration schedule and may not be the day immediately following Visit 3.1. Soliqua 100/33 administration for these participants should be 7 (± 2) days after their last weekly GLP-1 RA dose. A phone contact should be made to **participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation,** to remind them of the next morning's injection and to provide instructions for SoloStar pen use. The participants will provide their concomitant medication details to the site personnel over the phone.

[f] Doses of SU should be down-titrated by 50% when Soliqua 100/33 is started on Day 0.

[g] Weekly phone contacts for dose adjustments will be continued at the investigator's discretion until the desired fasting SMPG value is achieved.

[h] If the desired fasting SMPG value is not achieved in the first 8 weeks of treatment; the investigator has the option to continue weekly dose titration phone contacts for an additional 4 weeks (until Week 12) for the purpose of achieving glycemic targets.

[i] At the end of the study, participants should discuss with the investigator, in collaboration with their HCP, whether to continue on the Soliqua 100/33 treatment regimen or transition to an alternate antihyperglycemic therapy.

[j] An unscheduled visit can be planned anytime during the treatment period if IMP resupply is required. This can be a site visit or via phone contact with DTP IMP delivery. If DTP Soliqua 100/33 supply is required, the sponsor-approved courier company will need at least 72 hours' notice to collect Soliqua 100/33 treatment kits from a study site.

[k] Visit 2 will be performed at Day –15 for ALL participants, including those on weekly GLP-1 RA, who will administer their last dose 7 (± 2) days before the first dose of Soliqua 100/33; those taking daily SU (dose will be down-titrated by 50% on the morning of Soliqua 100/33 initiation); and those taking daily DPP-4i, and daily GLP-1 RA (oral or injectable; their last dose will be administered on the morning of Day –1, the day before the first dose of Soliqua 100/33).

[l] Body weight and height will be recorded during the screening period for the calculation of BMI (metric: BMI = weight (kg)/height [m^2]) and only body weight will be recorded during the baseline and at the end of the treatment period.

[m] Participants are required to measure fasting SMPG values before breakfast at least 3 to 4 times per week throughout the study period (to inform each dose adjustment) and record the results in the eDiary. During the titration period, fasting SMPG should be performed on each of the 3 to 4 days before each dose adjustment.

[n] HbA1c will be measured during the screening and run-in periods, and at Visit 3.1 (before administration of the meal) at the central laboratory, to determine study eligibility, and at the end of the 16-week treatment period (Visit 7), to determine change in glycemic control.

[o] Blinded CGM will be performed for 14 continuous days. The baseline CGM measure will be captured before discontinuing the daily (oral or injectable) or weekly GLP-1 RA, DPP-4i, or down-titration of SU by 50%, and before initiation of Soliqua 100/33 treatment. During the run-in period, CGM device reinsertion will be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8; Section 6.2.1). During the end of the treatment period, CGM device reinsertion will also be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8), if data can be captured during the 14-day end-of-treatment window (Section 6.2.1).

[p] The MMTT includes a standardized meal (ie, Boost Very High Calorie) that contains approximately 530 kcal and is composed of 19% carbohydrates, 44% protein, and 33% fat. The composition and the quantity of the standardized meal must be identical throughout the study period. Baseline MMTT is to be performed before discontinuation of daily (oral or injectable) or weekly GLP-1 RA, DPP-4i, or down-titration of SU medications. Participants on weekly GLP-1 RA should have their baseline MMTT conducted within 7 (± 3) days after their last dose. During the baseline (Visit 3.1), blood samples will be collected at the following time points: premeal (30 min) and just before administration of OADs or GLP-1 RA (oral or injectable) (baseline); time 0 (just before meal administration); 10 min; 20 min; and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 hours post-meal for plasma glucose, C-peptide, and insulin levels. At Visit 3.1, participants on OADs or an oral or injectable GLP-1 RA will be required to take their dose after blood sample for FPG and HbA1c is collected and 30 minutes before administration of the meal during the MMTT (during which measures for both β-cell function and PPG analyses will be captured). Soliqua 100/33 should be administered 30 minutes before administration of the meal during the MMTT at Visit 7 (during which only measures for PPG analyses will be captured). At the end of the treatment period (Visit 7), blood samples will be collected for plasma glucose levels, as follows: premeal (30 min) and just before administration of Soliqua 100/33; and time 0 (just before meal administration); 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 hours post-meal. These values will be used for PPG analyses with the goal of deriving reduction in maximum glucose exposure in the 4-hour period after the breakfast meal after Soliqua 100/33 administration at Week 16 compared with baseline.

[q] At baseline, the CGM device will be removed and the data will be downloaded on Day –1 at their next site visit (ie, Visit 3.1), after collection of C-peptide, insulin, and plasma glucose data from the MMTT. Downloaded CGM data will be reviewed by the investigator to determine participants' study eligibility. At the end of the treatment period, the CGM device will be removed and the data will be downloaded on the fifteenth day after CGM placement (ie, Visit 7; after collection of only plasma glucose data from the MMTT). Downloaded CGM data will be verified by the investigator at the site to determine participants' study completion.

[r] Participants with less than equivalent of 8 days of evaluable CGM data (not necessarily consecutive) of a 14-day period (eg, days of CGM device wear × % time CGM device active < 8) during the run-in period will be considered as screen failures.

[s] Participants will undergo the MMTT to assess maximum PPG exposure in the 4-hour period after the breakfast meal with biomarkers of β-cell function (plasma glucose, insulin, and C-peptide) measured at Visit 3.1 (ie, site visit during the baseline period), whereas only plasma glucose will be assessed at Visit 7 (ie, end of the treatment period).

[t] Participants should discontinue GLP-1 RA, DPP-4i, or down-titrate SU medications after all baseline assessments have been completed. SU doses should be down-titrated by 50% when starting Soliqua 100/33, whereas the last dose of daily DPP-4i and daily GLP-1 RA (oral or injectable) should be administered on the morning of Day –1, the day before the first dose of Soliqua 100/33. Participants on weekly GLP-1 RA should administer their last dose 7 (± 2) days before the first dose of Soliqua 100/33.

[u] Soliqua pen instructions will be given to all participants at Visit 3.1. A phone contact should be made to **participants on weekly GLP-1 RA** on the day **before Soliqua 100/33 initiation**, to remind them of the next morning's injection and to provide instructions for SoloStar pen use.

[v] For the scheduled site visits, participants are required to arrive fasting without administering the Soliqua 100/33 injection. Fasting is defined as no food intake in the 8 hours before blood sampling, except water.

[w] Baseline DM-SAT should be completed before discontinuation or down-titration of baseline therapies. The questionnaire should be completed at the start of the visit before any other study tests or procedures are performed or Soliqua 100/33 is administered.

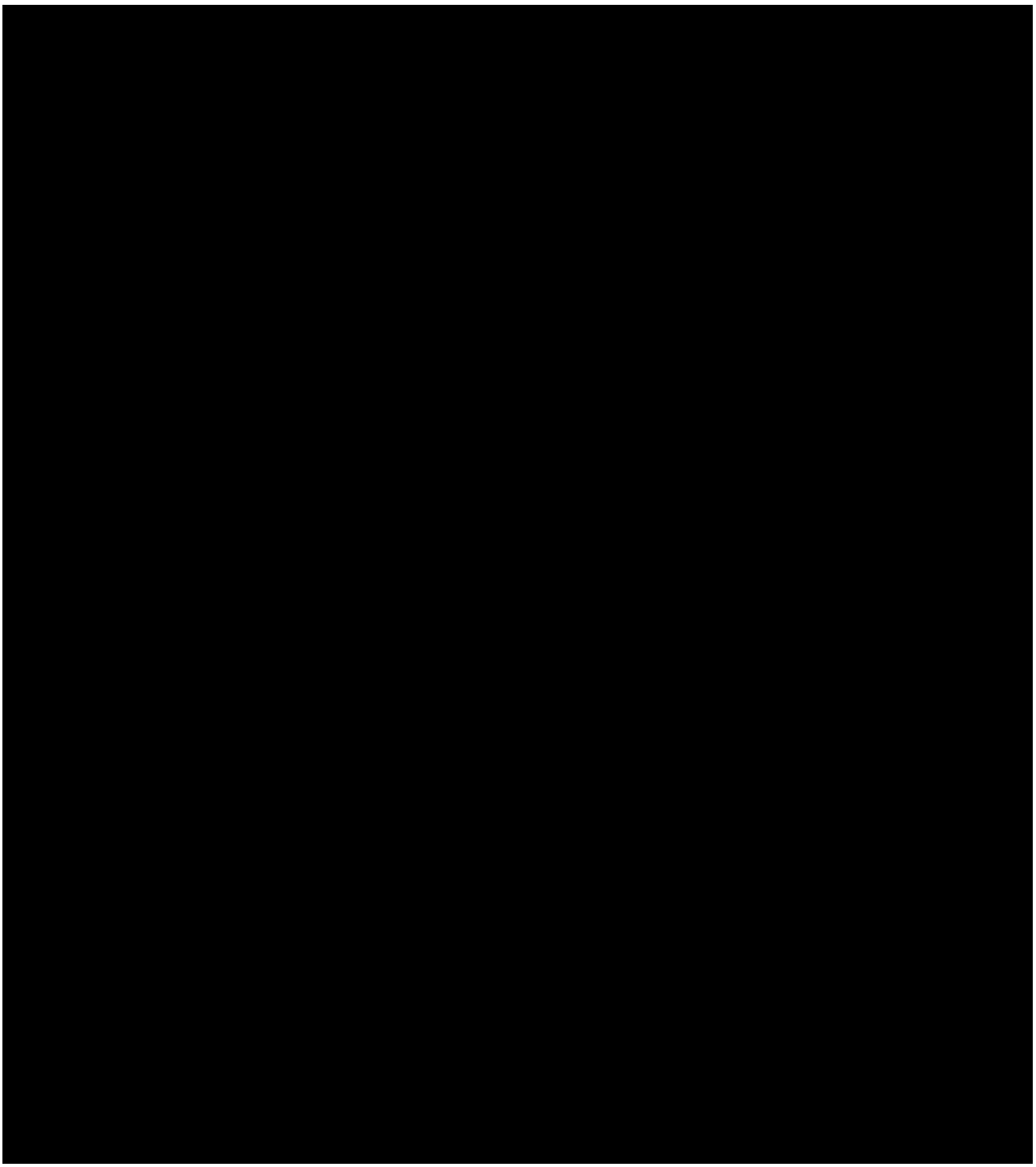
[x] The following hypoglycemia categories of interest will be presented: overall hypoglycemia and confirmed hypoglycemia (ADA Levels 1, 2, and 3; Section 6.3.2).

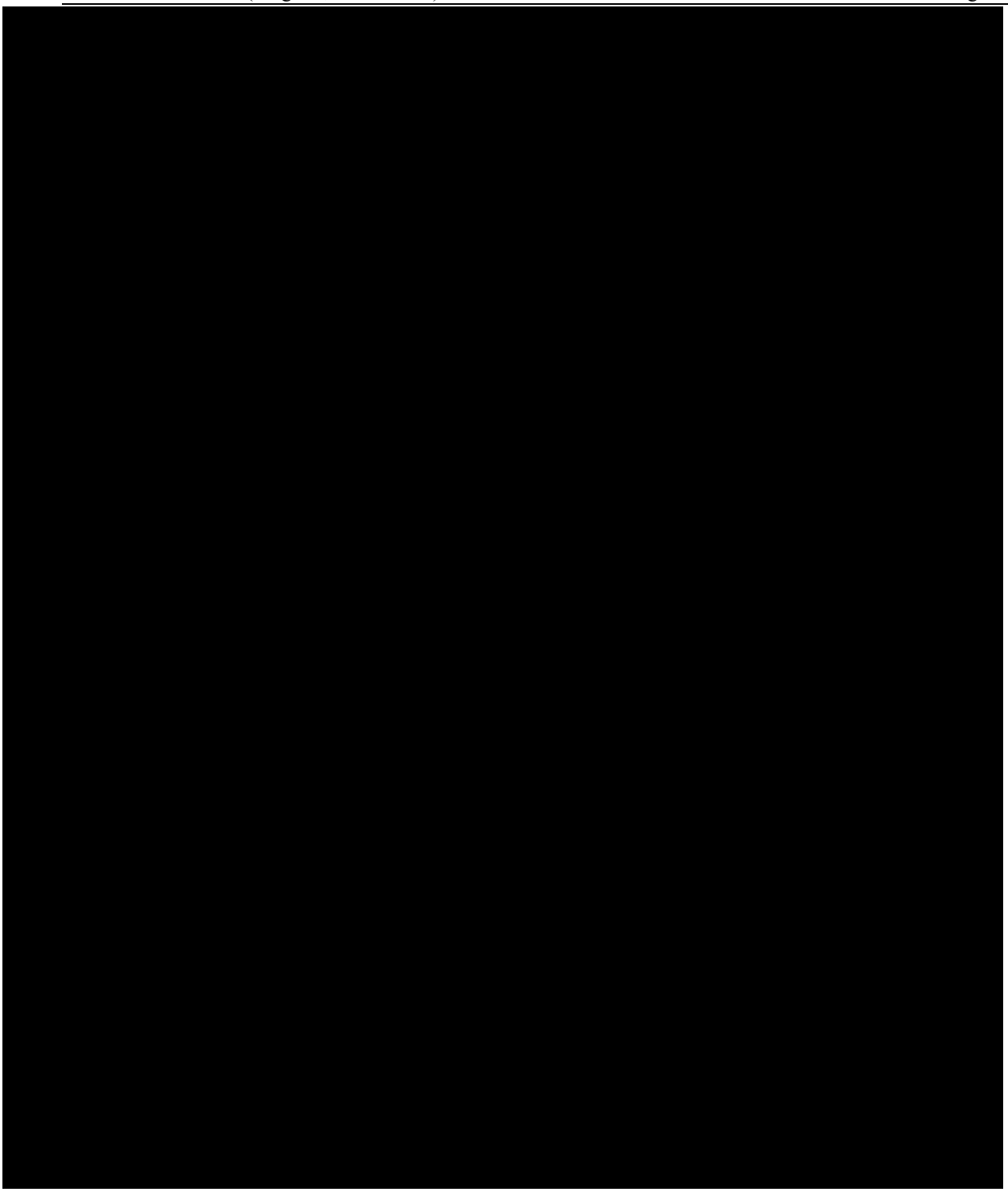
[y] Urinalysis: pH, glucose, ketones, leukocytes, blood/Hb, protein.

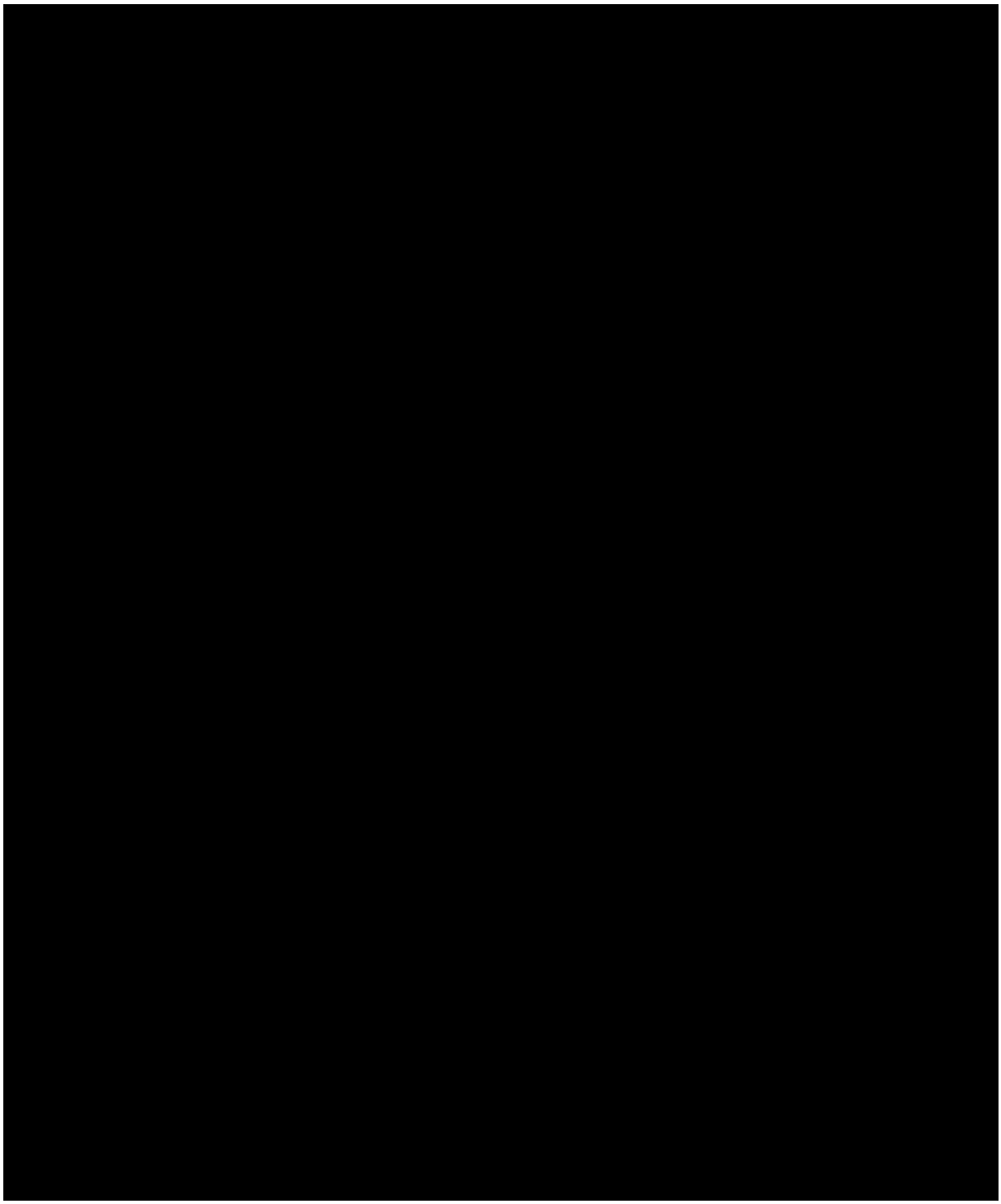
[z] Only for women of childbearing potential; urine pregnancy test.

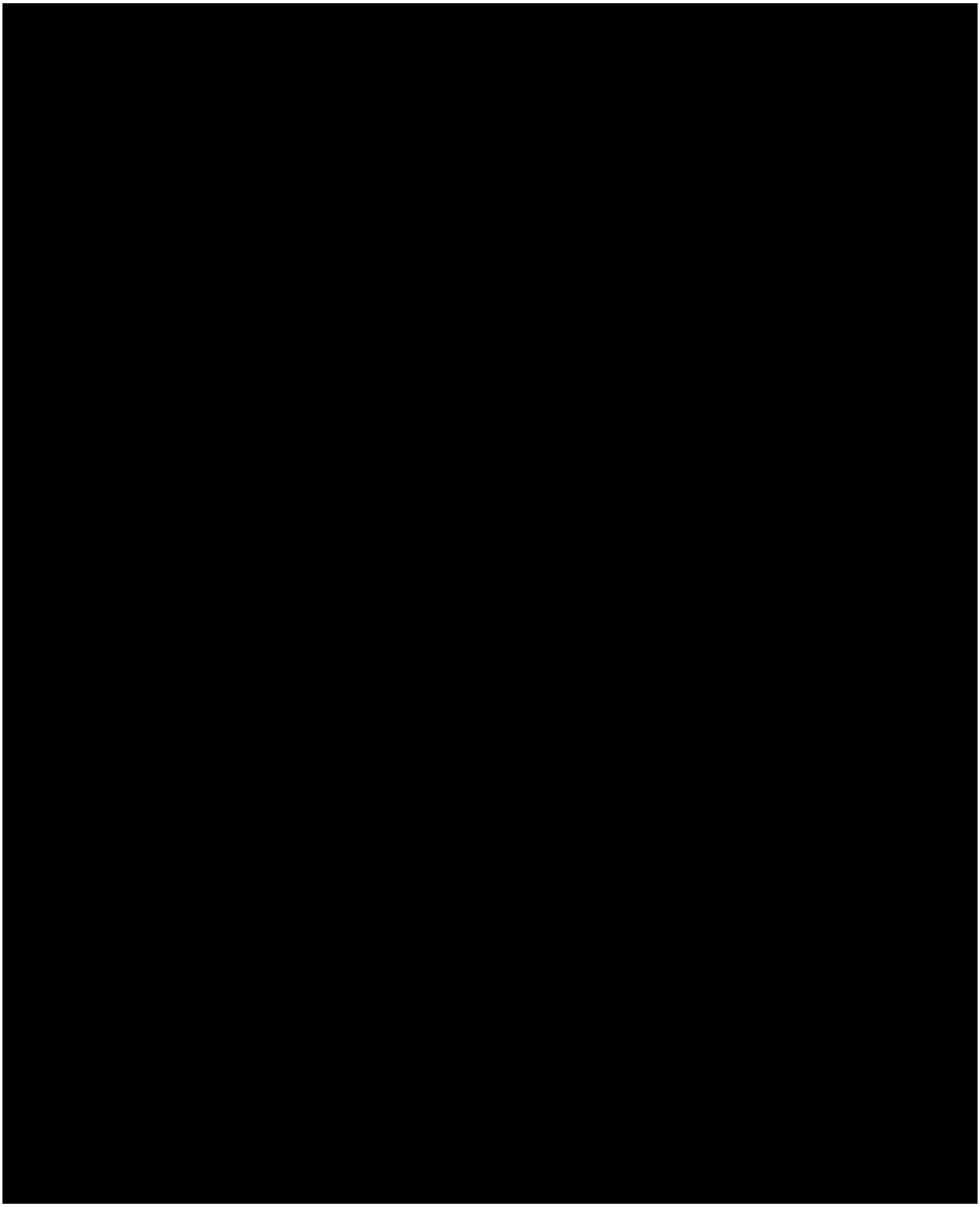
13.2 Appendix: Diabetes Medication Satisfaction Tool

(For information only)









13.3 Appendix: Participant eDiary Information

Participants will be provided with an eDiary to use during the study. Participants will be instructed on how to complete the eDiary.

eDiary completion will occur from the screening period (Visit 1) through the follow-up period (Visit 8). The participant is expected to return for site visits with the eDiary completed. The eDiary will be reviewed by the study site staff by viewing the data transmitted from eDiaries into the database.

The following information is to be recorded in the eDiary:

- Each dose taken (date/time and actual dose). The participant will document any temporary treatment discontinuations.
- Fasting SMPG values before breakfast at least 3 to 4 times per week throughout the study period (to inform each dose adjustment).
- Symptoms of hypoglycemia: Participants will be trained on the hypoglycemia eDiary completion requirements and the need to contact the investigator as soon as possible in case of a significant hypoglycemia occurrence, so that appropriate actions can be taken (eg, intolerance to the study drug injection).
- If assistance to resolve the hypoglycemia event was required out of necessity or convenience.

13.4 Appendix: Clinical Laboratory Tests

- The tests detailed in Table 13-2 will be performed by the central laboratory, except urine pregnancy tests, which will be performed at sites, using urine pregnancy test kits that are provided by the sponsor.

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

- Additional tests may be performed at a local or central laboratory at any time during the study as determined necessary by the investigator or required by local regulations. If they are used to evaluate an AE (diagnostic, follow-up, outcome), the results must be entered into the eCRF.

Table 13-2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments[a]	Parameter
Hematology	Erythrocytes
	Platelet count
	Leukocytes
	Hb
	Hematocrit
Clinical chemistry	AST
	ALT
	Alkaline phosphatase, total bilirubin (if >ULN, then the direct and indirect subfractions must be measured)
	Amylase
	Lipase
	Creatinine
	Uric acid
	Sodium
	Potassium
Urinalysis	pH
	Glucose
	Ketones
	Leukocytes
	Blood/Hb
	Protein
Calcitonin	Calcitonin

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eCRF, electronic case report form; Hb, hemoglobin; ULN, upper limit of normal.

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

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

13.5.1 Definition of AEs

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

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

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

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

Events NOT Meeting the AE Definition

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

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

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

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

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

13.5.2 Definition of SAEs

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

- **Results in death**

- **Is life-threatening**

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

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

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

AE and SAE Recording

- When an AE/SAE occurs, the investigator is responsible for reviewing all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to proactively send photocopies of the participant's medical records, except an autopsy report in the event of death, to the sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor's representative.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of an AE/SAE/AESI.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The investigator will also consult the prescribing information, for marketed products, in their assessment.
- For each AE/SAE/AESI, the investigator **must** document in the medical notes that they have reviewed the AEs/SAEs/AESIs and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator makes an assessment of causality for every event before initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

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

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

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

13.5.4 Reporting of SAEs

SAE Reporting to the Sponsor via an EDC Tool

- The primary mechanism for reporting an SAE to the sponsor's representative (ie, PPD Pharmacovigilance) will be the EDC tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see the following section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can

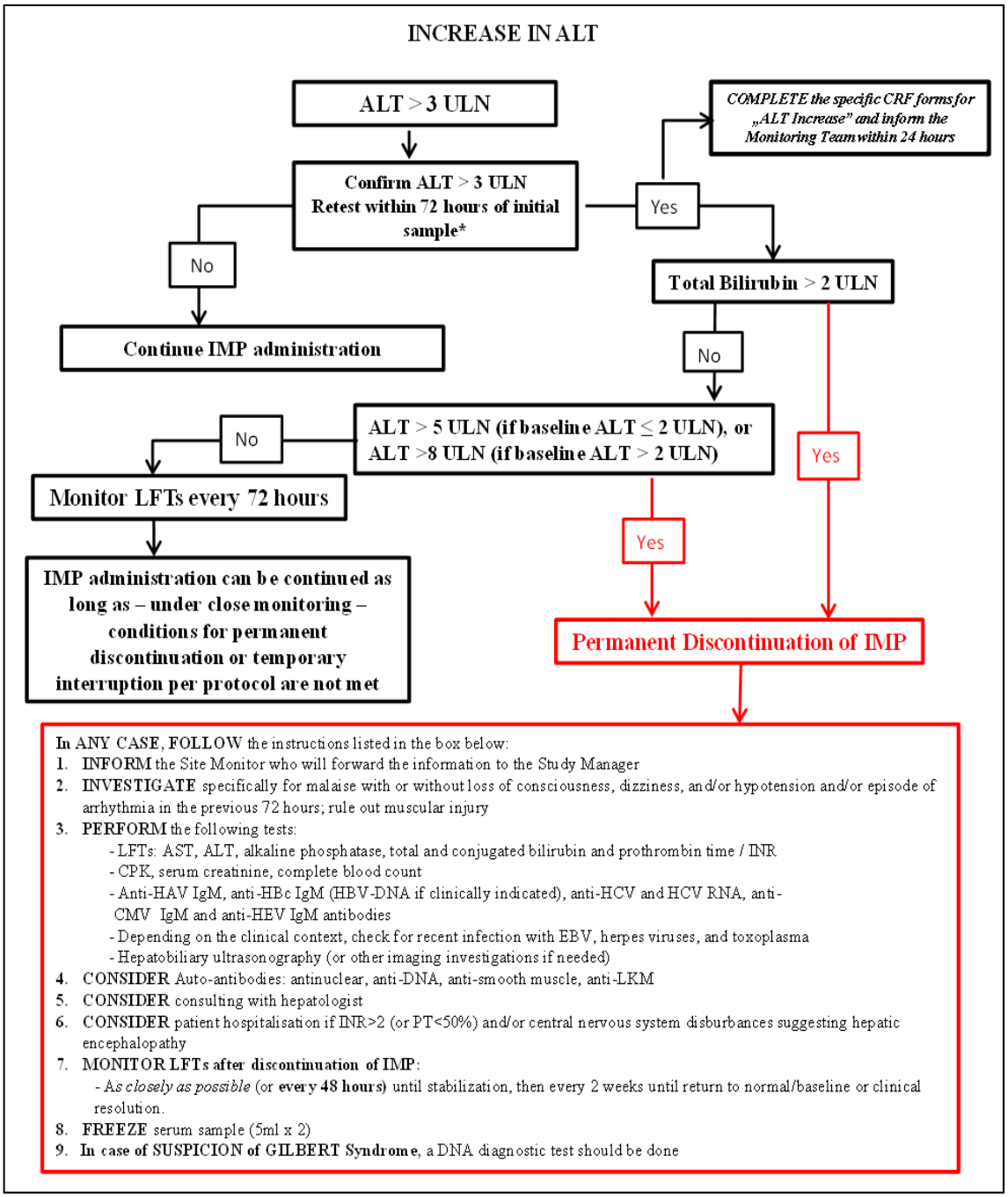
report this information on a paper SAE form (see the following section) or to the sponsor's representative by phone.

- Contacts for SAE reporting can be found in the Investigator's Study File.

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor's representative.
- In the unlikely event of EDC downtime, the paper forms must be used for reporting of events that require expedited reporting (SAEs/AESIs). Paper forms should be faxed to PPD Pharmacovigilance at 1-888-488-9697.
- Initial notification via fax does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator's Study File.

13.6 Appendix: Liver Safety



Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CMV, cytomegalovirus; CPK, creatine phosphokinase; CRF, case report form; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBc, hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus;

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

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

Notes:

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

Section 13.5 provides guidance on safety reporting.

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

13.7 Appendix: Contraceptive and Barrier Guidance

DEFINITIONS

Woman of Childbearing Potential

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

Permanent sterilization methods include the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.
- For individuals with permanent infertility due to a medical cause other than these procedures (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied in determining study eligibility.

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

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

Woman of Non-childbearing Potential

Women in the following categories are considered WONCBP:

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

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

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

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

Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal • Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • Oral • Injectable
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. [b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. [c] Male condoms must be used in addition to hormonal contraception. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

Collection of Pregnancy Information

Male Participants With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive Soliqua 100/33.

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

Female Participants Who Become Pregnant

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

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

- Although pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

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

- Any poststudy pregnancy-related SAE considered reasonably related to the investigational product by the investigator will be reported to the sponsor as described in Section 6.3.5.5. Although the investigator is not obligated to actively seek this information for former study participants, they may learn of an SAE through spontaneous reporting.

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

13.8 Appendix: Source Documents

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

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

DEFINITION OF SOURCE DATA

Source Data to Be Found in the Participant's File

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

- Agreement and signature of ICFs (Section 9.3) with the study identification and any privacy forms.
- Study identification (name).
- Treatment kit number, dates of administration, and doses of Soliqua 100/33 administered.
- Medical, surgical, and diabetes history, including information on the following:
    - Demography, inclusion, and exclusion criteria.
    - History of alcohol consumption and smoking.
    - Comorbidities.
    - Last participation in a clinical study.
    - Contraception method for WOCBP.
    - Previous and concomitant medications, including treatment for diabetes mellitus.
    - Dates and times of visits and assessments, including examination results.

  - Vital signs, height, body weight, and clinical laboratory reports.
  - AEs and follow-up.
- In case of an SAE, the site should file in the source documents, at least, copies of the hospitalization reports and any relevant examination reports documenting follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason.

Source documentation may be found in the following:

- Participant's identity (identification card or other verification document of participant identity).
- Medical history.
- Nursing notes.
- Physician's notes.
- Participant's eDiary.
- Glucometer.

Source Data Verification Requirements for Screen Failures

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

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

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

13.9 Appendix: Eligibility and Analysis Criteria for CGM Measurements

Eligibility Criteria

- Participants with less than equivalent of 8 days of evaluable CGM data (not necessarily consecutive) of a 14-day period (eg, days of CGM device wear × % time CGM device active < 8) during the run-in period will be considered as screen failures (Section 6.2.1).

- During the run-in period, CGM device reinsertion will be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8; Table 13-3 and Figure 13–1).

- During the end of the treatment period, CGM device reinsertion will also be allowed for participants who do not meet the equivalent of at least 8 days of evaluable CGM data (not necessarily consecutive) over a 14-day period as a result of premature sensor failure (eg, days of CGM device wear × % time CGM device active < 8), if data can be captured during the 14-day end-of-treatment window (Table 13-3 and Figure 13–1).

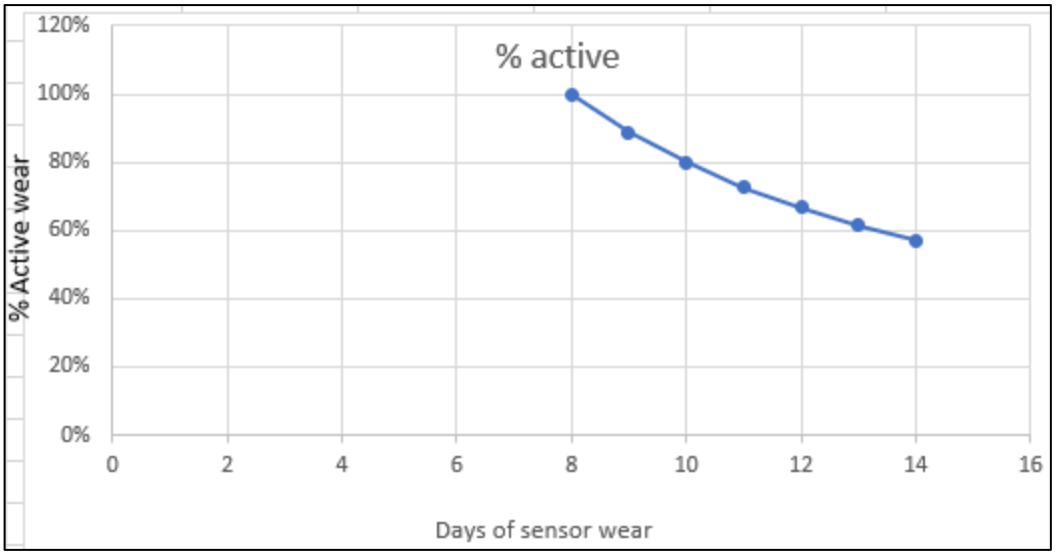
- For participants who discontinue study treatment prematurely, the visit window can be extended by 14 days to collect the CGM data before they permanently discontinue the treatment.

Table 13-3 Criteria for CGM Device Reinsertion

No. of Days CGM Device Worn[a]	Time CGM Device Active (%)[a]	Equivalent Days
8	100	8.00
9	89	8.01
10	80	8.00
11	73	8.01
12	67	8.04
13	62	8.01
14	57	7.98

Abbreviations: AGP, Ambulatory Glucose Profile; CGM, continuous glucose monitoring.
Note: Any combination of number of days of CGM device worn and % time CGM device is active that results in fewer than 8 equivalent days (defined as ineligibility) of evaluable CGM data will require device reinsertion.
[a] AGP report.

Figure 13–1 Criteria for CGM Device Reinsertion



Abbreviation: CGM, continuous glucose monitoring.

Analysis Criteria

- Endpoint data will be included in the analysis if at least 10 out of 14 days (not necessarily consecutive) have at least ≥80% of evaluable CGM data per 24-hour period during the run-in period as well as the end of the treatment period (ie, from Weeks 14 to 16).