NCT05114590

STATISTICAL ANALYSIS PLAN

Protocol 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**
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Compound number (INN/Trademark):	**HOE901/AVE0010** **Soliqua 100/33**
Study phase:	**Phase 4**
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VERSION HISTORY

This statistical analysis plan (SAP) for study LPS16990 is based on the protocol dated 18 Aug 2021. This section summarizes major changes to the statistical analysis features in the SAP. There are no major changes to the statistical analysis features in this SAP.

The first participant was enrolled on 27 January 2022. This SAP will be approved before database lock.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	28-Apr-2023	Not Applicable	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 4, 16 week, prospective, multicenter, interventional, open-label, single-arm study in insulin-naïve participants with very uncontrolled type 2 diabetes mellitus (T2DM) using blinded continuous glucose monitoring (CGM). The primary endpoint will assess the change of time in range (70-180mg/dL) between baseline and week 16 as measured by CGM in participants initiated on Soliqua 100/33. Background GLP-1RA (oral or injectable) and DPP-4i therapies will be discontinued prior to Soliqua 100/33 administration and sulfonylureas will be down-titrated by 50% when starting Soliqua 100/33. Continuous glucose monitoring measures will allow clinicians to frequently observe changes in glycemic control and variability including measures such as time in range (TIR), time below range (TBR) and time above range (TAR) with more granularity than the measure of HbA1c% alone. The Freestyle Libre Pro is a flash glucose monitoring device that collects glucose values every 15 minutes for up to 14 days. These values are charted into a single daily view, irrespective of the numbers of glucose values measured to provide a view of glycemic control and variability and assist clinicians for management of patients with diabetes.

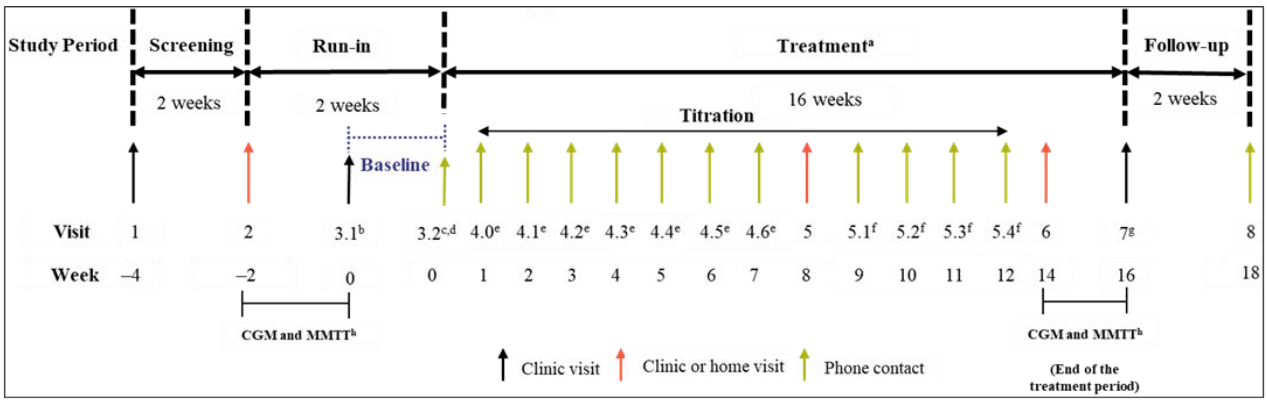
All eligible participants will undergo 14 days of blinded continuous CGM monitoring and a mixed-meal tolerance test (MMTT) during the run-in period while on background medications. Soliqua 100/33 will be initiated, and dose will be adjusted during the 12-week titration period, at the investigator's discretion, until the desired fasting self-measured plasma glucose (SMPG) value (80-100 mg/dL) is achieved.

In order to attain a target fasting SMPG value of 80 to 100 mg/dL dose of Soliqua 100/33 will be adjusted based upon the median SMPG value. 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. Doses will be adjusted by 2 to 4 units weekly, or at the investigators discretion to achieve targets. At Week 14, participants will again be required to undergo 14 days of blinded continuous CGM monitoring and a MMTT (only to derive PPG measures) at week 16. 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.

Should a participant not meet the CGM compliance criteria, reinsertion of the CGM device will be allowed.

A detailed description of the assessments performed during each study period and at each visit is provided in below figure (Figure 1)

Figure 1 - Graphical study design



Approximately 100 participants will be enrolled throughout 20 sites in the US.

Oral Antidiabetic Drugs (OAD)and Glucagon-Like-Peptide 1 Receptor Agonists (GLP-1RA)

All participants will be allowed to continue their background OADs (except DPP-4i and SU down-titration) at stable doses and administration timeframes throughout the study period, unless they must be stopped or modified for safety reasons. Any GLP-1RA use (oral or injectable) must also be discontinued prior to Soliqua 100/33 administration.

The analyses of the study will be conducted after completion.

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

	Objectives	Endpoints
Primary		
	• To demonstrate that in participants with T2DM failing to achieve glycemic control (HbA1c ≥9%-13%) on their current regimen of 2+ OADs with or without GLP-1RAs, 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

	Objectives	Endpoints
Secondary		
	Key Secondary Objective • To evaluate the impact of Soliqua 100/33 on measures of glycemic control and variability in participants with T2DM	**Key Secondary Endpoints** • 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 PPG exposure in the 4 hours after the breakfast meal (using MMTT data) • Change (%) from baseline to week 16 in TAR (>180 mg/dL)
	Secondary Objective • To evaluate the impact of Soliqua 100/33 on other measures of glycemic control and variability in participants with T2DM	**Secondary Endpoints** • Proportion (%) of participants 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, 12 am-6 am, and 6 am – 12 am) • Proportion (%) of participants achieving Glucose Management Indicator (GMI) <7% and <9% at week 16 • Change from baseline to week 16 in the 4 hour PPG $AUC_{0\text{-}4h}$ after start of the breakfast meal, including associated T_{max} (using MMTT data) • Proportion (%) of participants at week 16 who spend <15 minutes/day at a glucose level <54 mg/dL

Objectives	Endpoints
Tertiary/exploratory	
• To evaluate the impact of Soliqua 100/33 on additional measures of glycemic control and variability in participants with T2DM	• Change (mg/dL) from baseline to week 16 in mean of daily difference (MODD) • 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 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 • Association of participants reaching 60 units/day insulin glargine U100 and TIR >70% • Change in HbA1c percentage from baseline to week 16 • Change in the percentage from baseline to week 16 for Time in Tight Range (TITR)(70-140 mg/dL) • Proportion of participants with TIR (70–180 mg/dL) > 70% of each day at week 16 • Proportion of participants with ≥5% absolute improvement from baseline to week 16 in TIR (70–180 mg/dL) • Proportion of participants with ≥10% absolute improvement from baseline to week 16 in TIR (70–180 mg/dL) • Proportion of participants with improvement in HbA1c >0.5% points from baseline to week 16 without an increase in TBR (<54 mg/dL) of >0.5% • Proportion of participants with ≥10% absolute improvement from baseline to week 16 in TIR (70–180 mg/dL) without an increase in TBR (<54 mg/dL) of >0.5% • Proportion of participants with TIR (70–180 mg/dL) > 70% per day and TBR (<70 mg/dL) < 4% per day at week 16

	Objectives	Endpoints
	PRO Objective • To assess participant-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 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
		  ○ 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
		• Adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs)

1.2.1 Estimands

The primary estimand defined for main endpoints are summarized in Table 3. More details are provided in Section 4.

Table 3 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Analysis Set**	**Intercurrent event(s) handling strategy**	**Analysis Set-level summary (Analysis and missing data handling)**
Primary objective: To demonstrate that in participants with T2DM failing to achieve glycemic control (HbA1c ≥9%-13%) on their current regimen of 2+ OADs with or without GLP-1RAs, 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.				
Primary endpoint (treatment policy estimand)	Mean change in percentage of TIR at week 16 from baseline	Efficacy analysis set	Treatment policy strategy[a].	Mean and 95% (CI) of change in percentage of TIR at week 16 from baseline will be calculated for subjects who have CGM compliance at baseline and week 16. A one sample t-test will be applied to test the significance of changes.
Key Secondary objective: To evaluate the impact of Soliqua 100/33 on measures of glycemic control and variability in participants with T2DM				
Key Secondary endpoint (treatment policy estimand)	Mean percent changes of CV at week 16 from baseline	Efficacy analysis set	Treatment policy strategy[a]	Mean and 95% CI will be calculated for subjects who have CGM compliance at baseline and week 16. A one sample t-test will be applied to test the significance of changes.
	Mean mg/dL change of mean daily blood glucose at week 16 from baseline	Efficacy analysis set	Treatment policy strategy[a]	Mean and 95% CI will be calculated for subjects who have CGM compliance at baseline and week 16. A one sample t-test will be applied to test the significance of changes.
	Mean mg/dL change in maximum PPG exposure in the 4-hour period after the breakfast meal at week 16 from baseline	Enrolled analysis set	Treatment policy strategy[a]	Mean and 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.
	Mean percent change in TAR >180 mg/dL at week 16 from baseline	Efficacy analysis set	Treatment policy strategy[a]	Mean and 95% CI will be calculated for subjects who have CGM compliance at baseline and week 16. A one sample t-test will be applied to test the significance of changes.

a 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 and discontinuation of IMP

2 SAMPLE SIZE DETERMINATION

In LPS16990, a total of 100 participants will be enrolled in the study. Sufficient participants will be screened from 20 sites to include 100 participants, 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 (increase) in the percentage of TIR (70-180 mg/dL) from baseline to week 16 with sufficient power. A total sample size of 82 evaluable participants has 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

- Participants 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 participants 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 participants 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)

3 ANALYSIS SETS

The following analysis sets for analyses are defined:

Table 4 - Analysis Sets

Analysis Set	Description
Screened	All participants who signed the ICF.
Enrolled	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 compliant[a] CGM data at baseline.
Safety set	All enrolled participants who receive ≥1 dose of Soliqua 100/33.

a. CGM compliance is defined as 1) at least 8 out of 14 days (not necessarily consecutive) have 100% of evaluable CGM data per 24-hour period (at least 8 days with 96 records minimum per day) OR 2) at least 9 out of 14 days (not necessarily consecutive) have ≥89% of evaluable CGM data per 24-hour period (at least 9 days with 85 records minimum per day) OR 3) at least 10 out of 14 days (not necessarily consecutive) have at least ≥80% of evaluable CGM data per 24 hour period (at least 10 days with 77 records minimum per day)

4 STATISTICAL ANALYSES

The database lock will be performed when all participants have completed their follow-up phase. Final analyses in the clinical study report will be based on all data collected up to this database lock.

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), quartile ranges, median, minimum, and maximum.

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

Unless otherwise specified below, all confidence intervals (CI) will be two-sided at the 95% confidence level and displayed to the same level of precision as the statistic they relate to. If an estimate or a CI is not estimable, it will be presented as 'NE'. If neither an estimate, nor its CI are estimable, it will be presented as simply 'NE', not displaying 'NE' twice.

The p-values will be two-sided and will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as '<0.001'. If a p-value is greater than 0.999 it will be reported as '>0.999'.

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

The baseline value is defined as the last available value before the first injection of Soliqua 100/33. Participants enrolled but not treated will have a last available measurement following enrollment.

If multiple valid values of a variable (efficacy or safety) exist within a same day (and the recorded times of measurement do not identify which of them is the last assessment), the value measured during the scheduled visit will be used as Baseline in the analysis. If none of those values were assessed during a scheduled visit, then all these measurements will be used for the analysis and the average will be calculated to derive the baseline value.

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).

Baseline safety and baseline efficacy results are presented in the safety and efficacy analyses, respectively.

All safety analyses will be performed on the safety analysis set.

Statistical analysis will be performed using SAS Enterprise software Version 9.4 or higher.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration. There are two periods within pre-treatment period. A 2-week screening period and a 2-week run-in period.
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration during Visit 7 (Week 16).
- The **post-treatment period** is defined as the period from the end of the on-treatment period to the end of the 2-week safety period. (Week 18)

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis sets listed in Table 4 will be summarized. The participants excluded from the efficacy set will be displayed in a listing. A separate listing will be created for those who are excluded from the efficacy set due to technical issues from the CGM device.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled (i.e., do not have IMP dispensed subsequently). The number (%) of screen failures and reasons for screen failures will be provided in the screened set disposition descriptions.

The number (%) of participants in the following categories will be provided:

- Screened participants
- Enrolled participants
- Enrolled but not exposed participants
- Enrolled and exposed participants
- Participants who completed the 16-week study treatment period as per protocol
- Participants who completed the entire study period as per protocol (22 weeks).

- Participants who did not complete the study period as per protocol and did not record a main reason for study discontinuation
- The number (%) of exposed and non-enrolled participants will also be summarized.
- Final study status

Additionally, trial impact (disruption) due to COVID-19 will be summarized for the safety set using number and percentage. Participants for whom at least one of the following events occurred during the study will be presented:

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

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

The primary endpoint is the difference from baseline to week 16 in the percentage of TIR of 70-180 mg/dL using 14 days of CGM data at baseline. 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. All the efficacy assessments collected during the study will be used, including those obtained after IMP discontinuation or introduction of rescue therapy. Regardless of intercurrent events at week 16, the value for the mean change in the percentage of TIR will be used.

CGM data

CGM compliance is defined as:

1. at least 8 out of 14 days (not necessarily consecutive) have 100% of evaluable CGM data per 24-hour period (total of 768 records on 8 days) OR
2. at least 9 out of 14 days (not necessarily consecutive) have ≥89% of evaluable CGM data per 24-hour period (total of 768 records on 9 days and at least 9 days with 85 records minimum) OR
3. at least 10 out of 14 days (not necessarily consecutive) have at least ≥80% of evaluable CGM data per 24-hour period (total of 768 records on 10 days and at least 10 days with 77 records minimum)

during baseline (the run-in period) as well as week 16.

During the run-in period or end of treatment period, CGM device reinsertion will be allowed for participants who do not meet the compliance criteria over a 14-day period as a result of premature sensor failure.

Baseline will be defined as the first 14 evaluable days of evaluable CGM data prior to first day of treatment and referred to as the run-in period in the graphical study design. An evaluable day is defined as a 24-hour period with ≥80% non-missing measurements. Only evaluable days will be included in the analysis. Week 16 will be defined as the first 14 evaluable days of evaluable CGM data starting at day 95 or later.

The first day of CGM data will start at time of device insertion and subsequent days will start every 24 hours. If the device is re-inserted, device with the most compliant data will be used and if neither session is evaluable, the combined data from both sessions will be used as evaluable data. For subsequent reinsertions, the day will start at time of reinsertion.

Unless otherwise specified, outcome variables based on CGM data will use subjects in the efficacy analysis set with compliant data at baseline.

Percent time in the glucose range is defined as the total number of 15-minute increments where a participant's blood glucose falls within range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) divided by the total number of observed 15-minute increments in that period. Percent time in range will be calculated for baseline (run-in) and for week 16.

4.3.2 Main analytical approach

Mean change (in percentage) from baseline and its associated 95% CI will be calculated using subjects in the efficacy analysis set with compliant baseline CGM data. A one-sample t-test will be applied to test the significance of changes at week 16 over baseline (run-in). The statistical test will be a 2-sided at a nominal 5% significance level.

Hypothesis Testing of the Primary Endpoint

H0: There is no improvement in TIR at week 16 compared with baseline.

H1: There is an increase in TIR at week 16 compared with baseline.

A two-sided 95% CI will be presented, superiority versus baseline will be demonstrated if the lower bound is above 0.

Missing data will be handled differently in accordance with the reasons for missing data. If the missing data are due to technical issues with the CGM device (ie, CGM data are not evaluable as per the CGM compliance rule Section 4.3.1 during the 2-week run-in period [baseline] 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 all other reasons the Week 16 assessment will be imputed with the baseline observation carried forward (BOCF); therefore, change from baseline will be 0.

The MCAR assumption will be non-conclusively evaluated by testing the association between the baseline covariates and missing data status at Week 16. Specifically, a contingency table will be constructed based on the missing data status at Week 16 and a given categorical baseline covariate. If all the expected cell counts exceed 5, the association will be tested by chi-square test; otherwise, Fisher's exact test will be used.

4.3.3 Sensitivity analyses

As a sensitivity analysis, the primary analysis will be repeated to include participants with any missing data due to discontinuation or non-compliant data at Week 16 by imputing with BOCF. The mean and its associated 95% CI will be reported.

As a second sensitivity analysis, the primary analysis will be repeated for all participants in the efficacy analysis set. All missing data at Baseline and Week 16 will be excluded and not imputed, and only compliant CGM data will be utilized. Mean and its associated 95% CI will be reported.

4.3.4 Supplementary analyses

No analysis is planned.

4.3.5 Subgroup analyses

The primary analysis will be replicated, if the number of participants in a specific subgroup is at least 20, for the following subgroups:

- Participants using OAD only at baseline
- Participants using OAD plus GLP-1RA at baseline
- Participants ≥ 65 years of age
- Participants < 65 years of age.

In these subgroup analyses, mean (SD) and associated 95% CI, as well as minimum, median, and maximum will be provided.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Key/Confirmatory secondary endpoint(s)

4.4.1.1 Definition of endpoint(s)

Key Secondary Endpoints:

- Change (%) from baseline (run-in) to week 16 in glucose total CV. The data for this endpoint come from the CGM data using the glucose readings. The endpoint will be calculated globally (percent change from the total two weeks baseline CV to the two weeks end of treatment week 16 CV). The CV formula used is $CV\%_{total} = \frac{SD_{total}}{\bar{x}} * 100\%$ where $SD_{total} = \sqrt{\frac{\sum(x_i - \bar{x})^2}{n-1}}$, x_i is the individual glucose reading value, $\bar{x}$ is the 14-day mean and n is the number of data points and the % change will be reported. The alternative hypothesis to be tested is that the CV differs between baseline and week 16. A two-sided 95% CI will be presented.
- Change (mg/dL) from baseline (run-in) to week 16 in mean daily blood glucose. These data come from the CGM data and will be calculated for each day by using the average blood glucose for week 16 compared to the parallel day during the run-in period (baseline) [for example, Day 1 of baseline's average blood glucose will be compared to Day 1 of week 16's average blood]. A global average will be computed to determine the average of the mean daily blood glucose for the 14 days at baseline and also at week 16. The global average will be used for hierarchal testing and the mg/dL change will be reported. The alternative hypotheses to be tested is that mean daily blood glucose differs between baseline and week 16. Two-sided 95% CIs will be presented.
- Change (mg/dL) from baseline (run-in) to week 16 in the maximum PPG exposure in the 4 hours after the breakfast meal during the mixed-meal tolerance test collected from the CRF. The analysis is focused on the 4-hour interval at both baseline (run-in) and week 16 from t=0 (the timepoint at which glucose measurement is taken immediately preceding meal administration) throughout the subsequent 4 hours. For each participant, the overall maximum glucose value (mg/dL) within the described 4-hour period will be determined, and the difference between the maximum glucose value at baseline(run-in) and week 16 will be reported. The alternative hypothesis to be tested is that the maximum PPG differ between baseline and week 16. A two-sided 95% CI will be presented. This analysis will be based on participants in the enrolled set who have non-missing outcomes at baseline.
- Change (%) from baseline (run-in) to week 16 in TAR (>180 mg/dL). The percentage of time spent above the glycemic target range will be calculated as 100 times the total number of 15-minute increments of CGM data where a participant's blood glucose falls above normal range (>180 mg/dL) in a 14-day period divided by the total number of 15-minute increments read (up to 1344 15-minute increments). This will be calculated for

baseline (run-in) and for week 16 and the change will be reported. The alternative hypothesis to be tested is that the TAR differs between baseline and week 16. A two-sided 95% CI will be presented.

4.4.1.2 Main analytical approach

The key secondary estimand will be estimated based on the efficacy analysis set using measurements obtained during the study, regardless of intercurrent events. All four endpoints are continuous and will be summarized using the number of observations available, mean, SD, minimum, median, and maximum. 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 values will be provided, and the analysis will be tested with 2-sided tests at 5% significance level.

Key Secondary endpoints will undergo hierarchal testing in the order displayed in Section 4.6, using two-sample t-test. The results of the test will be displayed in a summary table.

Missing data handling of key CGM secondary endpoints will follow the same approach as the primary estimand.

Regarding participants who discontinue treatment early, but complete the early termination visit per protocol and have MMTT collected at the EOT visit, their data will be used if collected on study day 56 or later; otherwise, the week 16 outcome will be imputed. If the week 16 MMTT data were collected prior to day 56 or missed, then the week 16 outcome will be imputed using baseline observation carried forward (BOCF).

4.4.2 Supportive secondary endpoint(s)

Mean changes for continuous outcomes for other measures of glycemic control and variability:

- Proportion (%) of participants achieving total CV <36% at week 16. To calculate the proportion of participants achieving CV <36%, a sum of the number of participants with CV <36% divided by the total number of participants. The endpoint will be calculated using all CGM glucose readings available throughout each day for two weeks (week 14-16). As this is a binary outcome the endpoint will be summarized with proportions and 95% CI using the Clopper-Pearson exact method. A two-sided 95% CI will be presented.
- Change (%) from baseline (run-in) to week 16 in TIR [70-180 mg/dL] for specific time blocks [12 am – 6 am, 6 am – 12 pm, 12 pm – 6 pm, 6 pm - 12 am, and 6 am – 12 am]. The end point will find the percentage of time spent in the glycemic target range. This is 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 per time block and comparing the corresponding time blocks from week 16 to baseline in a 14-day period to determine change. Two-sided 95% CIs will be presented.
- The proportion (%) of participants achieving Glucose Management Indicator [GMI] <7% and <9% at week 16. The GMI (%) formula used is 3.31 + 0.02392 *(mean glucose in mg/dL from CGM data) (Bergenstal et al., 2018); this step is followed by determining the

number of participants achieving <7% and <9% at week 16. The endpoint will be calculated using all CGM data available throughout each day of the two-week period (week 14-16) for derivation of mean glucose. A two-sided 95% CI will be presented.

- Change from baseline (run-in) to week 16 in the 4-hour PPG area under the concentration time curve from 0 to 4 hours ($AUC_{0\text{-}4h}$) after start of the breakfast meal, including determination of the time to reach maximum associated concentration (T_{max}), are both based on MMTT data. T_{max} will be calculated by finding the time that corresponds to the maximum glucose concentration from t=0 over the 4 hrs. The 4 hour PPG AUC will be calculated from the glucose values measured at time 0 (just before the meal), 0.5 hours, 1.0 hours, 1.5 hours, 2.0 hours, 2.5 hours, 3.0 hours, and 4.0 hours post-meal utilizing the "trapezoidal rule" $AUC = \sum_{i=0\ hr}^{4\ hr} \frac{[Cgluc(i+1) + Cgluc(i)]}{2}(t_{i+1} - t_i)$ where C=concentration, i = specified time intervals in the MMTT, and t=time. Differences in ($AUC_{0\text{-}4h}$) from baseline (run-in) to week 16 will be reported as well as the corresponding T_{max} at baseline and week 16. Two-sided 95% CIs will be presented. This analysis will be based on participants in the enrolled set who have non-missing outcomes at baseline and week 16.
- Proportion (%) of participants at week 16 who spend < 15 minutes/day at a glucose level <54 mg/dL. The endpoint will be summarized based upon CGM data reporting both percentages and 95% CI using the Clopper Pearson exact method. A two-sided 95% CI will be presented.

Measures of glycemic control and variability will be presented at baseline and at the end of the treatment period (Week 16). The mean (SD) and associated 95% CI, as well as minimum, median, and maximum values will be provided.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

Mean changes for continuous outcomes for additional measures of glycemic control and variability in participants with T2DM:

- Change (mg/dL) from baseline (run-in) to week 16 in mean of daily difference [MODD] of glucose levels. Using the formula: $\frac{\sum_{t=0}^{t=95} ||[Day_{j+1}{}_t - Day_{j}{}_t]||}{number\ of\ paired\ timepoints}$ where t=time period in the 24 hour day by 15 minute intervals and j = day to calculate MODD for each participant 13 times comparing Day 2 to Day 1, up to Day 14 to Day 13 for Baseline and for week 16. The average absolute daily differences at each 15-minute interval of CGM data will be summarized using descriptive statistics. Two-sided 95% CI will be presented.
- Change (%) from baseline (run-in) to week 16 in TAR >250 mg/dL. The percentage of time spent above the glycemic target range will be calculated as 100 times the number of the total number of 15-minute increments of CGM data where a participant's blood glucose falls above normal range (>250 mg/dL) in a 14-day period divided by the total number of 15-minute increments read (1344 number of 15-minute increments). This will

be calculated for baseline and for week 16 to report the difference. A two-sided 95% CI will be presented.

- Change (%) from baseline (run-in) to week 16 in TBR <70 mg/dL. The percentage of time spent below the glycemic target range will be calculated as 100 times the number of the total number of 15-minute increments from CGM data where a participant's blood glucose falls below normal range (<70 mg/dL) in a 14-day period divided by the total number of 15-minute increments read (1344 number of 15-minute increments). This will be calculated for baseline and for week 16 to report the difference. A two-sided 95% CI will be presented.
- Correlation of change in percentage of TIR [70 – 180 mg/dL] and change in PRO from baseline (run-in) to week 16. Analysis will be done between each of the 4 domains (well-being, medical control, lifestyle, and convenience), PRO overall, and change in TIR. The purpose of finding the correlation of change from baseline to week 16 for percentage of TIR and PRO is to determine the relationship between those two continuous variables.
- Correlation of percentage of TIR [70 – 180 mg/dL] and HbA1c percentage achieved at week 16. The correlation of percentage of TIR and HbA1c achieved at week 16 will estimate the relationship between the two variables.
- Association of participants reaching 60 units/day insulin glargine U100 and TIR > 70%.
- Change in HbA1c percentage from baseline (run-in) to week 16. The alternative hypothesis to be tested is that the HbA1c will decrease from baseline to week 16. A two-sided 95% CI will be presented. This analysis will be based on participants in the enrolled set who have non-missing outcomes at baseline and week 16.
- Change in the percentage from baseline (run-in) to week 16 for TITR (70-140 mg/dL). The end point will determine the percentage of time spent in the glycemic tight target range. This is calculated as 100 times the number of recorded measurements in the glycemic target range, (70-140 mg/dL) inclusive, divided by the total number of recorded measurements per time block and comparing week 16 to baseline over a 14-day period to determine change. A two-sided 95% CI will be presented.
- Proportion (%) of participants with TIR (70–180 mg/dL) > 70% each day at week 16. To calculate the proportion of participants achieving TIR of >70% each day, a sum of the number of participants with more than 67 15-minute intervals with glucose values in range per day for all compliant days divided by the total number of participants. The endpoint will be calculated using all CGM glucose readings available throughout each day for two weeks at the end of study. As this is a binary outcome the endpoint will be summarized with proportions and 95% CI using the Clopper Pearson exact method. A two-sided 95% CI will be presented.
- Proportion (%) of participants with ≥5% absolute improvement from baseline in TIR (70-180 mg/dL). Absolute improvement is defined as an increase in TIR from baseline to week 16. To calculate the proportion of participants achieving ≥5% in TIR absolute improvement from baseline a sum of the number of participants with a positive percent change ≥5% will be divided by the total number of participants. The endpoint will be calculated using all CGM glucose readings available throughout each day for each two-

week time blocks. As this is a binary outcome the endpoint will be summarized with proportions and 95% CI using the Clopper Pearson exact method. A two-sided 95% CI will be presented.

- Proportion (%) of participants with ≥10% absolute improvement from baseline in TIR (70-180 mg/dL). Absolute improvement is defined as an increase in TIR from baseline to week 16. To calculate the proportion of participants achieving ≥10% absolute improvement in TIR from baseline a sum of the number of participants with a positive percent change ≥10% are divided by the total number of participants. The endpoint will be calculated using all CGM glucose readings available throughout each day for each two-week time blocks. As this is a binary outcome the endpoint will be summarized with proportions and 95% CI using the Clopper Pearson exact method. A two-sided 95% CI will be presented.
- Proportion (%) of participants with improvement in HbA1c >0.5% points without an increase in TBR (<54 mg/dL) of >0.5%. Improvement is defined as an increase in HbA1c from baseline to week 16. To calculate the proportion of participants achieving >0.5% improvement of HbA1c from baseline and with < 0.5 % change in TBR participants will be summed then divided by the total number of participants. The endpoint will be summarized based upon CGM data reporting both percentages and 95% CI using the Clopper Pearson exact method. A two-sided 95% CI will be presented.
- Proportion of participants with ≥10% absolute improvement from baseline in TIR (70-180 mg/dL) without an increase in TBR (<54 mg/dL) of >0.5%. Absolute improvement is defined as an increase in TIR from baseline to week 16. A sum of participants with both ≥10% of improvement from baseline in TIR and no increase in TBR of more than 0.5% will be divided by the total number of participants. The endpoint will be summarized based upon CGM data reporting both percentages and 95% CI using the Clopper Pearson exact method. A two-sided 95% CI will be presented.
- Proportion of participants with TIR (70–180 mg/dL) >70% and TBR (<70 mg/dL) <4% at Week 16. To calculate the proportion of participants achieving TIR >70% and TBR <4%, a sum of the number of participants with both TIR >70% and TBR <4% divided by the total number of participants. The endpoint will be summarized based upon CGM data reporting both percentages and 95% CI using the Clopper Pearson exact method. A two-sided 95% CI will be presented.
- Change in diabetes medication treatment-related impact and satisfaction, as measured by the DM-SAT, from baseline (run-in) to week 16. The four DM-SAT subscales/domains provide a means for the researcher or clinician to understand which component(s) of diabetes treatment were most responsive to an intervention, distinguish one treatment approach from another, or determine which were appraised more positively or negatively by a patient. DM-SAT questionnaire is comprised of 16-item measurements within 4 subscales/domains: well-being; medical control; lifestyle; convenience
  - Well-being – physical symptoms, mood, and energy.
  - Medical control – how well the medication(s) keep a participant's blood sugar where the participant thinks it should be, how often are "highs" avoided in a blood sugar test

according to the participant, and how much the participant feels in control of their diabetes.

- Lifestyle - how easy it is for a participant to have a lifestyle they prefer with the diabetes medication they are taking, how much a participant has to plan their social life around their diabetes medication(s), how much a participant plans their physical activity around their diabetes medication(s), how much a participant has to plan their mealtimes because of their diabetes medication(s), and how much time they spend each day on their diabetes medication.
- Convenience - how often are "lows" avoided in a blood sugar test according to the participant, the convenience of their diabetes medication(s) when they are traveling or away from home for more than one day, the way they take their diabetes medication(s), the time(s) of day they must take their diabetes medication(s), and the overall convenience of their diabetes medication(s).

The expectation is that the satisfaction scores will increase from baseline to week 16. Two-sided 95% CIs will be presented. These analyses will be based on participants in the enrolled set who have non-missing outcomes at baseline and week 16.

4.5.2 Main analytical approach

The correlation between TIR and participant-reported outcomes (PRO) and TIR and HbA1c at week 16 will be assessed using Pearson's correlation coefficient. A contingency table will be constructed based on TIR > 70% and participants requiring 60 units/day of insulin glargine at week 16. If all the expected cell counts exceed 5, the association will be tested by chi-square test; otherwise, Fisher's exact test will be used.

Mean (SD) and associated 95% CI, as well as minimum, median, and maximum values will be provided for continuous variables for change from baseline. The correlation endpoint tables present "n" being number of participants (xx) and correlation coefficient value (0.xxx). For correlation between change in TIR and PRO, a table will present PRO data for overall scores and subscale/domain scores and a 95% CI. Participants with non-compliant or missing data at week 16 will be excluded from the analysis.

For change in diabetes medication treatment-related impact and satisfaction, as measured by the DM-SAT, at baseline (run-in) and week 16, the mean (SD) and associated 95% CI, as well as minimum, median, and maximum values will be presented for overall score and by subscales/domains. The 16-item questionnaire is measured from 0-10: 0 = Not at all satisfied, 1-3 = Not too satisfied, 4-6 = Somewhat satisfied, 7-9 = Very satisfied, 10 = Extremely satisfied. The score for each the 4 domains/subscales is calculated as follows: lifestyle (sumscore lifestyle of 5 questions)/50; medical control (sumscore medical control of 3 questions)/30; convenience (sumscore convenience of 5 questions)/50 and well-being (well-being sumscore of 3)/30. The overall score will be calculated by: (sumscore overall of 16 questions)/160. If there are more than 25% missing items for a scale, the scale will be treated as missing. For the greatest measurement precision, it is recommended to use the full 16-item DM-SAT total score to assess overall treatment satisfaction in research applications, as a study outcome. There will be no reverse scoring as it is not applicable to the DM-SAT items.

A summary descriptive analysis of TIR, TAR, and TBR will be provided with no imputation for missing data. This will be provided under the Descriptive Analyses tables.

4.6 MULTIPLICITY ISSUES

A hierarchical testing procedure will be performed. Key secondary endpoints will be evaluated with a one-sample two-sided t-test ($t = \frac{\bar{x}-\Delta}{\frac{s}{\sqrt{n}}}$) to determine whether there is any change between baseline (run-in) and week 16. The overall type-I error rate will be controlled at the two-sided 0.05 level using a sequential testing procedure. For any secondary endpoints to be eligible for being declared significant, the primary endpoint must be significant at 0.05 significance level. The secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at 0.05 significance level of the previous one. The following key secondary endpoints will be tested in the following order:

- Change (%) from baseline to week 16 in coefficient of variation
- 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 (MMTT)
- Change (%) from baseline to week 16 in TAR (>180 mg/dL)

If at any step the null statistical hypothesis is not rejected, the endpoints listed after that step will be reported at nominal level, otherwise will be technically eligible for being declared significant.

A summary table will present the mean, 95% CI, p-value, and the statistical significance for the primary endpoint and the key secondary endpoints.

4.7 SAFETY ANALYSES

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

- The analysis of the safety variables will be analyzed descriptively, and no testing is planned. Planned analysis is described in further detail below.

The safety endpoints include number of participants with adverse events (AE), serious adverse events (SAEs), adverse events of special interest (AESIs), overall hypoglycemia, and confirmed hypoglycemia.

Hypoglycemia rates during 16 weeks of treatment, including the percentage of participants with at least 1 hypoglycemia event and number of events per participant year, will be analyzed descriptively in a table. Further explanation is described below in hypoglycemia section.

4.7.1 Extent of exposure

The extent of study treatment (specifically, insulin glargine) exposure and adherence will be assessed based on the safety set, presented by the following parameters:

- Duration of treatment;
- Mean planned dose, i.e., doses documented in CRF Exposure page;
- Mean actual dose, i.e., doses recorded in diary by participants;
- Minimum planned dose;
- Maximum planned dose;
- Last planned dose, i.e., the planned dose documented in CRF at the last visit;
- Number of participants whose planned dose reached at least 60 units/mL.

The lixisenatide dose will not be presented; instead, a footnote that states the ratio of insulin glargine (in unit/mL) to lixisenatide (in µg/mL) equals 3:1 will be included wherever applicable.

Duration of IMP exposure

The duration of IMP exposure will be calculated as date of the last IMP injection – date of the first IMP injection + 1. If the date of the last dose of IMP (in the eCRFs) is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively using descriptive statistics and categorically as below:

- ≤ 8 weeks
- > 8 weeks to ≤ 16 weeks
- >16 weeks

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

A summary of the number and percentage of subjects with any visit impacted by the COVID-19 pandemic may be produced, if applicable. The summary will include the number of visits and assessments impacted, as well as the reasons for the impacted visits/assessments.

Treatment adherence

A given administration will be considered nonadherent 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.

The adherence rate for a participant will be defined as the total number of days with a Soliqua 100/33 injection divided by planned number of days with Soliqua 100/33 injection multiplied by 100.

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

4.7.1.1 Overall exposure

The exposure information will be assessed by the following variable(s):

- Duration of IMP exposure (in weeks) is defined as (Last day of exposure – first day of exposure +1)/7.

4.7.2 Adverse events

All AEs will be collected from the signing of the ICF until the follow-up visit.

General common rules for adverse events

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

The AEs (which are recorded on the AE eCRF page, including hypoglycemia events qualifying as AEs) will be categorized as:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period, defined as the time from the signed informed consent date up to the first administration of the IMP.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period defined as the time from the first administration of the IMP (on Day 1) to the last administration of the IMP + 3 days.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period defined as the time starting 1 day after the end of the TEAE period up to the end of the study follow-up (2 weeks after the end of treatment period)

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

Pre-treatment safety data will be analyzed using the Screening Analysis Set. Treatment-emergent and post-treatment safety data will be analyzed using the Safety Analysis Set.

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

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

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

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

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose within the intended therapeutic interval (planned treatment period), adjusted according to the tested drug. Cases of symptomatic overdoses will constitute AESIs and will be listed as such.

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

Table 5 - Sorting of AE tables

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

a Sorting will be based on the mg dose intervention group/overall incidence.
b Within each table the sorting will be by the internationally agreed SOC order and decreasing frequency of PTs; in case of tie for PT, the sorting will be alphabetical.

Analysis of all AEs

The overview of TEAE with the details below will be generated (number and percentage of participants) in a table:

- Any TEAE
- Any treatment emergent SAE
- Any treatment emergent AESI
  - Pregnancy.
  - Symptomatic overdose.
  - Increase in ALT (>3 × ULN).
- TEAE leading to death (death as an outcome of the AE as reported in the AE page)
- Any TEAE leading to temporary IMP discontinuation.
- Any TEAE leading to permanent IMP discontinuation

- Any treatment-related TEAE
- Any TEAE leading to study discontinuation

The overview summary for TEAEs will be provided on the safety set and will be repeated on the subgroup of safety participants according to trial impact (disruption) due to the COVID-19 pandemic.

Individual listings (AEs, SAEs, AEs leading to death, TEAEs leading to permanent IMP discontinuation, AESI, AEs for Treated and not enrolled participants) will be provided to support the summary tables based on the safety set.

A listing of all participants who died during the study will be provided.

The AE summaries of Table 6 will be generated with number (%) of participants experiencing at least one event.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
Common TEAE (≥5%)	Primary SOC and PT
TEAE related to IMP	Primary SOC, and PT
TEAE by maximal severity	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
TEAE leading to study discontinuation	Primary SOC and PT
TEAE leading to permanent discontinuation of IMP	Primary SOC and PT
TEAE leading to death	Primary SOC and PT
Pre-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any, any AEs leading to death, any AEs leading to permanent IMP discontinuation and be repeated for participants impacted by COVID-19

Analysis of adverse events of special interest (AESIs)

An adverse event of special interest (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. All AESIs will be reported to the Sponsor in the same timeframe as SAEs (within 24 hours).

Adverse events of special interest (AESIs) are defined by the protocol and will be documented in eCRF:

- 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.
- Symptomatic overdose (serious or nonserious) with IMP/NIMP.
- Increase in ALT (>3 × ULN).

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 7. The number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 5.

Table 7 - Selections for AESIs

AESIs	Selection
Symptomatic overdose	eCRF specific tick box on the AE page
ALT Increase	eCRF specific tick box on the AE page
Pregnancy	eCRF specific tick box on the AE page

4.7.3 Hypoglycemia events

During the study, participants are to be instructed to document any hypoglycemic episodes in their e-diary. Hypoglycemia will be reported on the specific eCRF page with onset date and time, symptoms and/or signs, the glucose measurement obtained at the time of the event before countermeasures, the collection date and time of glucose measurement, and the treatment of hypoglycemia. Hypoglycemia meeting the definition of an adverse event will be documented, in addition, on the AE form in the eCRF.

The following hypoglycemia events are the categories of interest:

- Any Hypoglycemia Event: Any event recorded in Hypoglycemic Event Information Library eCRF page that has “Yes” as the response to the question “Were any hypoglycemic events experienced”, regardless of the plasma glucose measurements.
- ADA Level 1 Hypoglycemia: A measurable glucose concentration of <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) that can alert a person to take action. A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a marker of physiologic 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. The event will be captured if the Glucose Measurement in the Hypoglycemic Event Information Library eCRF page falls within the described blood glucose concentration levels.

- ADA Level 2 Hypoglycemia: 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. The event will be captured if the Glucose Measurement in the Hypoglycemic Event Information Library eCRF page falls within the described blood glucose concentration levels.
- ADA Level 3 Hypoglycemia: A severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery due to participant's inability to help themselves. Severe hypoglycemia captures events during which the symptoms associated with hypoglycemia affect a participant such that the participant requires assistance from others. The event will be captured if the Glucose Measurement in the Hypoglycemic Event Information Library eCRF page falls within the described blood glucose concentration levels and if "Required Assistance because subject was not capable of helping self was selected.
- Documented Hypoglycemia: (<70 mg/dL): a glucose level of <70 mg/dL (or <3.9 mmol/L) (with or without symptoms).
    - Documented Symptomatic Hypoglycemia (<70 mg/ dL): defined as an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than 70 mg/dL (3.9 mmol/L). Clinical symptoms that often result from a hypoglycemic episode can include (but not necessarily limited to) increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma.
    - Documented Symptomatic Hypoglycemia will be identified in the Hypoglycemic Event Information Library eCRF page in those who indicated "symptoms were present" with a measured plasma glucose value <70 mg/dL (or <3.9 mmol/L)
        - Documented Serious Symptomatic Hypoglycemia: defined as an event where the participant also requires assistance from another person for recovery due to participant's inability to help themselves, i.e., identified in the Hypoglycemic Event Information Library eCRF page, as "Required assistance because subject was not capable of helping self".
        - Documented Non-serious Symptomatic Hypoglycemia: defined as an event where the participant does not require assistance from another person for recovery, i.e., identified in the Hypoglycemic Event Information Library eCRF page, with a "No Assistance" response or "Received Assistance but Subject Was Capable of Helping Self".
    - Documented Asymptomatic Hypoglycemia: asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration < 70 mg/dL (or <3.9 mmol/L) i.e., identified in the

Hypoglycemic Event Information Library eCRF page with a "No" response to "Were symptoms present".

- Symptomatic Hypoglycemia: defined as any symptomatic hypoglycemia recorded on Hypoglycemic Event Information Library eCRF page responding that symptoms were present with the plasma glucose measurements of < 70 mg/dL (or <3.9 mmol/L).
- Pseudohypoglycemia: defined as any symptomatic hypoglycemia recorded on Hypoglycemic Event Information Library eCRF page responding that symptoms were present with the plasma glucose measurements of ≥ 70 mg/dL (or ≥3.9 mmol/L).

Hypoglycemia events categorized by time of day at which the event occurred by ADA levels, will be provided in a table:

- Nocturnal Hypoglycemia Defined by Time of the Day: Any hypoglycemia event that occurs between 00:00 and 05:59, regardless of whether the participant was awake or woke up because of the event.
- Nocturnal Hypoglycemia Defined by Sleep Status: Any hypoglycemia event that wakes the participant from sleep between bedtime and rising in the morning, i.e., before the morning assessment of fasting prebreakfast SMPG and before any insulin injection. The participant wakes up because of the event.
- Daytime Hypoglycemia Defined by Time of the Day: Any hypoglycemia event that occurs between 06:00 and 23:59.
- Daytime Hypoglycemia Defined by Awake Status: Any hypoglycemia event that occurs between the participant waking up and going to sleep.

Hypoglycemia observation periods

- Pre-treatment hypoglycemia events are events that developed or worsened or became serious from the signed informed consent date up to first administration of the IMP.
- Treatment-emergent hypoglycemia events are those that developed or worsened or became serious during the on-treatment period arising from the time of the first IMP administration (on Day 1) up to 1 day after the last IMP injection.
- Post-treatment hypoglycemia events are events that developed or worsened or became serious during the post-treatment period arising 1 day after the end of the TEAE period up to the end of the study follow-up (2 weeks after the end of treatment period)

Descriptive analysis will summarize hypoglycemia events in a table (repeat for subgroups [i.e., OAD only at baseline, OAD plus GLP-1 RA at baseline, ≥ 65 years of age, < 65 years of age]):

- Overall number and percentage of participants with at least 1 hypoglycemia event (for overall and each observation period) and number of hypoglycemic events (for overall and each observation period)
- Number and percentage of participants with at least 1 hypoglycemia event and number of hypoglycemic events, by ADA classification levels

- Number and percentage of participants with at least 1 hypoglycemia event and number of hypoglycemic events, by observation periods
- Documented Hypoglycemia
  - Documented symptomatic hypoglycemia
    - Documented serious symptomatic hypoglycemia
    - Documented non-serious symptomatic hypoglycemia
  - Asymptomatic Hypoglycemia
- Symptomatic Hypoglycemia
- Pseudohypoglycemia
- Nocturnal Hypoglycemia Defined by Time of the Day, overall and by ADA levels
- Nocturnal Hypoglycemia Defined by Sleep Status, overall and by ADA levels
- Daytime Hypoglycemia Defined by Time of the Day: overall and by ADA levels
- Daytime Hypoglycemia Defined by Awake Status, overall and by ADA levels

In addition, rate of on-treatment symptomatic hypoglycemic events (Overall, and by time of day per ADA levels) will be summarized in a table whereas

Hypoglycemic events rate per participant year = Number with hypoglycemic events/Total Person Years

If there are multiple events from an individual participant, all events will be counted.

where Total PY is calculated as below:

Observation period	Total Person Years	Time to event (days)	Censoring time (days)
On-treatment	(cumulative total time to event date for participants with event + cumulative total of censoring time for participants without event)	date of event -first dose date +1	(last dose date+1) -first dose date +1

Participants with symptomatic hypoglycemia events, and participants with severe hypoglycemia events will be displayed in listings. A figure will be provided showing the time to the first severe or documented ADA Level 3 symptomatic hypoglycemia during on-treatment period.

4.7.4 Additional safety assessments

4.7.4.1 Laboratory variables and vital signs

The following laboratory variables and vital signs will be converted into standard international units and analyzed from screening to week 16 per the schedule of events. Analysis will distinguish

between early end of treatment and week 16 end of treatment. Glucose values will be analyzed using conventional units.

- Hematology:
  - Red blood cells and platelets: erythrocytes, platelet count, leukocytes, hemoglobin, hematocrit
- Clinical chemistry:
  - Metabolism: lipase, amylase
  - Electrolytes: sodium, potassium
  - Renal function: creatinine, uric acid
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin (if >ULN , then the direct and indirect subfractions must be measured)
- Calcitonin
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, ketones, leukocytes, blood/hemoglobin, protein and glucose
- Vital signs: pulse rate, systolic and diastolic blood pressure, weight

Specified in the study protocol, all clinical safety laboratory assessments will be performed by a central laboratory. 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. A urine pregnancy test will be performed at each schedule of event timepoint and treated as an AESI and not reported in the laboratory analysis tables.

Quantitative analyses

Descriptive statistics will be used for results and changes from baseline will be provided for each planned visit, during the on-treatment period. Laboratory values below the lower limit of quantification (LLOQ) will be set to one half of the LLOQ.

4.7.4.2 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 must be reported in association with an AE or SAE.

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

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

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

- Any product complaint
- Any product complaint related to AEs

In addition, the analysis below will be conducted.

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

4.8 OTHER ANALYSES

4.8.1 Descriptive Analyses

Other summary descriptive analyses will be provided based upon the efficacy assessments. This includes a summary descriptive analysis of TIR, TAR, TBR, fasting plasma glucose, and two analyses based on fasting self-monitoring plasma glucose value (SMPG) taken in the mornings 3-4 times per day, 3 days before visit to determine titration. This information is provided from the eDiary. The analyses for fasting SMPG will be based on data from week -2 to week 16 showing a descriptive analysis of both lowest and average SMPG of each.

4.8.2 Biomarker analyses

β-cell biomarker analyses fall outside this SAP. β-cell markers (glucose, insulin, and C-peptide) will be collected at baseline only during the MMTT at specific timepoints during Visit 3.1. These values will be utilized to model β-cell function by an external clinician once the trial is completed and the data are available.

4.9 INTERIM ANALYSES

No interim analysis is planned.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF 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
CGM: continuous glucose monitoring
CI: confidence interval
CV: coefficient of variation
DM-SAT: Diabetes Medication Satisfaction Tool
DPP-4i: dipeptidyl peptidase-4 inhibitor
eCRF: electronic case report form
GLP-1RA: glucagon-like peptide 1 receptor agonist
GMI: Glucose Management Indicator
HbA1c: glycated hemoglobin
HLGT: high level group term
HLT: high level term
HRQoL: health related quality of life
ICF: informed consent form
IMP: investigational medicinal product
LLOQ: lower limit of quantification
LLT: lower-level term
MCAR: missing completely at random
MedDRA: medical dictionary for regulatory activities
MMTT: mixed-meal tolerance test
MODD: mean of daily difference
OAD: oral antidiabetic drug
OC: observed cases
PPG: postprandial glucose
PRO: patient reported outcome
PT: preferred term
SAE: serious adverse event
SAP: statistical analysis plan
SD: standard deviation
SMPG: self-measured plasma glucose
SOC: system organ class
SU: sulfonylurea
T2DM: type 2 diabetes mellitus
TAR: time above range, time above range
TBR: time below range
TE: treatment emergent
TEAE: treatment-emergent adverse event

TIR: time in range
TITR: Time in Tight Range
T_{max}: time to reach maximum concentration
ULN: upper limit of normal
WHO-DD: World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

There are no changes to protocol-planned analyses.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

5.3.1 Protocol deviations

Significant protocol deviations, including drug dispensing irregularities, will be summarized in the enrolled analysis set. Protocol deviations due to the COVID-19 pandemic will be categorized as such. Protocol deviations will come from the clinical trial management system and will be categorized according to the rules document for protocol deviations.

A listing of participants with at least one significant protocol deviation will be provided with comprehensive information related to each deviation identified.

5.3.2 Demographics and baseline characteristics

Treatment adherence, demographics, and baseline characteristics will be summarized in descriptive tables. Continuous data will be summarized using the number of observations available, mean, SD, quartile ranges, minimum, median, and maximum. Categorical data will be summarized using count and percentage.

Baseline safety and efficacy parameters will be presented along with the safety and efficacy summaries.

The following demographics and baseline characteristics will be summarized:

- age in years as continuous variable and in categories of 65 ≤ and > 65
- gender (Male, Female)
- race: White, Black or African American, Asian (will subgroup Asian with Chinese, Japanese, Asian Indian, Korean, Other Asian Origin, Multiple Asian Origin, Asian Origin Not Reported, Asian Origin Unknown), Other, Multiple, Not Reported, Unknown.
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown, Other Ethnicity)
- weight (kg)

- height (cm)
- BMI in kg/m^2 as documented in eCRF and in categories BMI ≤ 30 (kg/m^2) and BMI > 30 (kg/m^2)
- OAD status (OAD with GLP-1RA or OAD without GLP-1RA)

5.3.3 Medical or surgical history

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

Specific disease history, including gestational diabetes, will be reported in the summary.

Comorbidities will be summarized separately. Comorbid disease will be summarized from eCRF pages on the physical exam page completed by investigators based on participant report. Body system will be examined as assessment and defined as normal, abnormal, or not done.

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

5.3.4 Disease characteristics at baseline

The following baseline disease characteristics will be summarized (see Section 5.4.1 for calculation details):

- HbA1c background %
- Renal Function (measured in creatinine and uric acid)
- Background medication.
- Duration of diabetes
- Age at onset T2DM

Any technical details related to computation, dates, and imputations for missing dates are described in Section 5.4.2.

Continuous data will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum for enrolled participants. Categorical and ordinal data will be summarized using the number and percentage of enrolled participants.

5.3.5 Prior and concomitant medication

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

- Prior medications are those the participant used prior to first IMP administration. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any interventions received by the participant concomitantly to the IMP during the on-treatment period/from the first administration of IMP to the last IMP administration + 1 day.
- Post-treatment medications are those the participant took in the timeframe spanning the last IMP administration +2 days (week 16) up to the end of the study (Week 18).
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as a post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the enrolled set, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence. In case of equal frequency, alphabetical order will be used. Participants will be counted once each ATC category (anatomic or therapeutic) linked to the medications.

Use of all concomitant medications will be recorded in the participant's eCRF. 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.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 Demographic formulas

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

5.4.2 Disease characteristics formulas

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

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

5.4.3 Reference dates

For efficacy analyses, Day 1 reference date is a participant's enrollment date. For safety assessments, the Day 1 reference date is a participant's first treatment date.

5.4.4 Missing Data

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

Medication missing/partial dates

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

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

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

Missing date and time of first IMP administration

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

The exposure duration should be kept as missing.

Missing severity of adverse events

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

5.4.5 Timepoint assessment

Diary Timepoint Definitions

At Visit 3.1 (Day -1), participants on OADs or an oral or injectable GLP-1RA 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 and measures for both β-cell function and PPG analyses will be captured. β-cell function (plasma glucose, insulin, and C-peptide) will be collected at baseline and only plasma glucose will be collected at week 16. Participants on a weekly GLP-1RA should have their baseline MMTT conducted within 7 (± 3) days after their last dose and administer their last weekly GLP-1RA dose 7 (± 2) days before the first dose of Soliqua 100/33. During Visit 3.1(on the morning of Day –1, the day before the first dose of Soliqua 100/33), the last doses of daily DPP-4i and daily GLP-1RA should be

administered. Down-titration of SU dose to 50% should occur at Visit 3.2 (when starting Soliqua 100/33).

Participants are enrolled into the trial at Visit 3.2, which is considered Day 1. The first dose of Soliqua 100/33 is administered at this visit (Visit 3.2).

Visit windows

All post-baseline data (e.g. CGM data, MMTT data, patient reported outcome data, laboratory data, physical exam data, and vital signs data) will use windowing to determine the analysis visit.

The visit windows will consider nominal visits and unscheduled visits within the window. If there are two visits within a window, then the visit closest to the target day will be used.

Table 8 – Visit Windows for non-CGM data

Week	Target Day	Days
Week -4	-28	informed consent date to -15
Week -2	-15	-14 to -1
First treatment	1	1
Week 8	57	2 to 60
Week 14	99	61 – 102
Week 16	113	103 – 116

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-1RA, 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-1RA 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-1RA (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-1RA 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 be made to **participants on weekly GLP-1RA** 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-1RA, 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-1RA (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-1RA, 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 CGM compliance criteria. During the end of the treatment period, CGM device reinsertion will also be allowed for participants who do not meet the CGM compliance criteria.
[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-1RA, DPP-4i, or down-titration of SU medications. Participants on weekly GLP-1RA 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-1RA (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-1RA 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 who do not meet CGM compliance criteria at baseline will be considered 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-1RA, 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-1RA (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-1RA 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-1RA** 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.

5.5 APPENDIX 5 DEVIATIONS FROM PLANNED STUDY CONDUCT

This section summarizes major statistical changes in the current protocol version.

Table 9 - Major statistical changes from approved version of protocol

Protocol Version	Protocol Version Date	Deviations from Protocol	Rationale
1.0	18-Aug-2022	changing the endpoint to Correlation of Change in the Percentage of TIR (70 180 mg/dL) and Patient Reported Outcome (PRO) from Baseline to Week 16	TIR is subject level and LS means of the PRO is not subject level, it is best not to use correlation
		Updating endpoint correlation of participants reaching 60 units/day insulin glargine U100 and TIR >70% to reaching 60 units and TIR > 70% and testing as a chi-square test instead of a correlation analysis.	Association 60 units and TIR > 70% are binary variables
		Update CGM compliance definition to include 8 days with 100% data available in a 24- hour period and 9 days with 89% of data available in a 24-hour period for both baseline and week 16.	The decision to update compliance rule is to allow the best opportunity for participants to be included in the efficacy analysis set to ensure we meet the best power available for sample size.

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