Statistical Analysis Plan: I8B-MC-ITSW (Version 1)

A Study of LY900014 in Participants with Type 2 Diabetes using Continuous Glucose Monitoring

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1. Statistical Analysis Plan: I8B-MC-ITSW: A Study of LY900014 in Participants with Type 2 Diabetes using Continuous Glucose Monitoring

LY900014

Study I8B-MC-ITSW (ITSW) is a Phase 3b, prospective, open-label, outpatient, multicenter, single-treatment-group study conducted in participants with T2D currently treated with a basal bolus analog MDI regimen.

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Protocol I8B-MC-ITSW
Phase 3b

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

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3. Revision History

This statistical analysis plan (SAP) is the first version and is based on the protocol of I8B-MC-ITSW approved on 21 April 2020 and the following amendments (a) approved on 13 July 2020. This SAP was approved prior to the first patient visit.

4. Study Objectives

Table ITSW.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate time glucose values from continuous glucose monitoring (CGM) are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period with LY900014 treatment	• Percentage of time with CGM glucose values between 70-180 mg/dL (3.9-10.0 mmol/L) (both inclusive) during daytime period with 14 days of CGM use at Week 12 compared with baseline
Gated Secondary	
• To evaluate HbA1c	• HbA1c change from baseline to Week 12
• To evaluate time glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the 24-hour period with LY900014 treatment	• Percentage of time with CGM glucose values between 70-180 mg/dL (3.9-10.0 mmol/L) (both inclusive) during the 24-hour period with 14 days of CGM use at Week 12 compared with baseline
Other Secondary	
• To evaluate time in hypoglycemic glucose ranges, obtained from CGM use	• Percentage of time with CGM glucose values <54 mg/dL (<3.0 mmol/L) during daytime and 24-hour periods with 14 days of CGM use at Week 12 compared with baseline
• To evaluate time in hyperglycemic glucose ranges, obtained from CGM use	• Percentage of time with sensor glucose values >180 mg/dL (>10.0 mmol/L) and >250 mg/dL (>13.9 mmol/L), during daytime and 24-hour periods with 14 days of CGM use at Week 12 compared with baseline

• To evaluate postprandial incremental AUCs, obtained from CGM use	• Postprandial incremental $AUC_{0\text{-}1\ hour}$ and incremental $AUC_{0\text{-}2\ hour}$ at Week 12 compared with baseline
• To evaluate proportion of participants achieving HbA1c targets	• The proportion of participants with HbA1c <7% and ≤6.5% at Week 12
• To evaluate bolus, basal, and total daily insulin dose	• Bolus, basal, and total insulin doses and bolus/total insulin ratio at Week 12 compared with baseline
• To evaluate severe hypoglycemia	• Incidence of severe hypoglycemia events from baseline to Week 12
• To evaluate insulin treatment satisfaction regarding glycemic control as measured by the ITSQ	• Change from baseline in ITSQ glycemic control domain scores at Week 12
Tertiary/Exploratory	
• To evaluate proportion of participants achieving CGM-based glycemic targets	• The proportion of participants with percentage of time in target CGM glucose range (70-180 mg/dL [3.9-10.0 mmol/L]) >70%, time in hypoglycemia (<54 mg/dl [<3.0 mmol/L]) <1%, and time in hyperglycemia (>250 mg/dL [>13.9 mmol/L]) <5% with 14 days of CGM use at Week 12
• To evaluate glucose profiles, obtained from CGM use	• Average glucose for a 24-hour period from each 14-day CGM session at Week 12 compared with baseline
• To evaluate glucose variability, obtained from CGM use	• CV with 14 days of CGM use at Week 12 compared with baseline
• To evaluate insulin treatment satisfaction as measured by the ITSQ	• Change from baseline in ITSQ total and domain scores (except glycemic control domain) at Week 12

• To characterize participants' willingness to incorporate LY900014 into diabetes management routine	• Distribution of responses to study mealtime insulin experience question at Week 12
• To evaluate attitudes towards diabetes technology use as measured by the DSAT	• Change from baseline in DSAT total score at Week 12

5. Study Design

5.1. Overall Design

Study ITSW is a Phase 3b, prospective, open-label, outpatient, multicenter, single-treatment-group study conducted in participants with type 2 diabetes (T2D) currently treated with a basal-bolus analog multiple dose injection (MDI) regimen. Participants will use unblinded continuous glucose monitoring (CGM) (Freestyle Libre 14-day system) for diabetes management and glucose data collection during the study. The study is designed to evaluate the time sensor glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) with 12 weeks of LY900014 treatment.

LY900014 will be injected immediately (0-2 minutes) prior to each meal in combination with insulin glargine U-100 (Basaglar®) as basal insulin. Basal-bolus insulin doses will be titrated to achieve protocol glucose targets during the study.

5.2. Sample Size Determination

Approximately 167 participants will be assigned to treatment with LY900014 such that 150 participants complete the study through the primary endpoint at Week 12.

The primary objective of this study is to evaluate the change of time glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period from baseline to endpoint at Week 12 with LY900014 treatment.

This sample size has approximately 80% power to detect an increase of 4.5% time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period from baseline, assuming no true difference in time in target range between baseline and endpoint, and a standard deviation (SD) of 19.5%. Assuming a 10% dropout rate for 12 weeks, approximately 167 participants will need to be assigned.

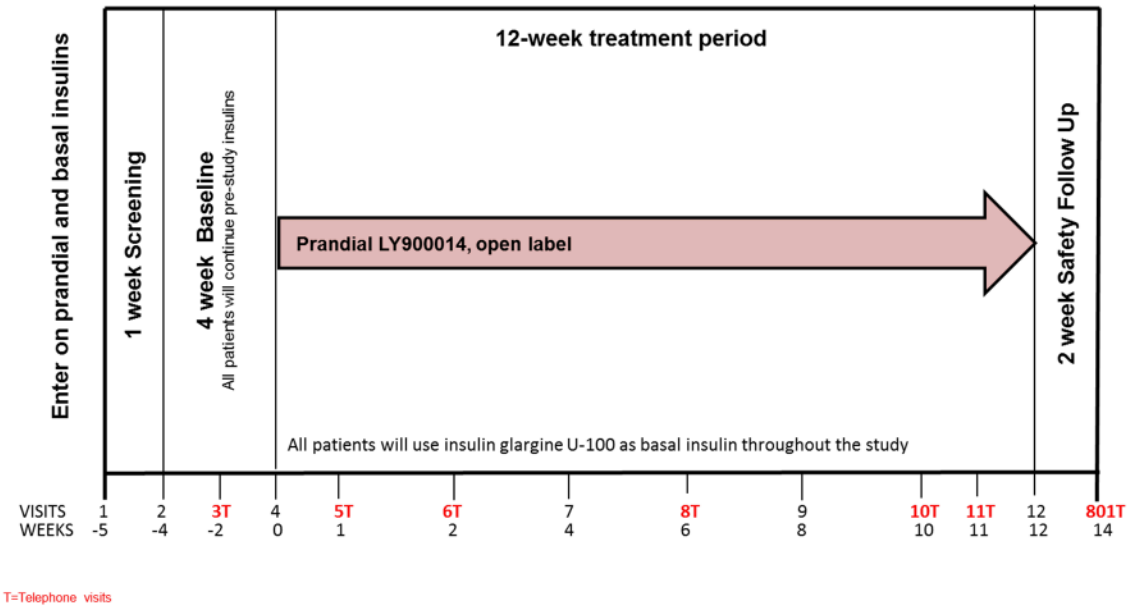

Figure ITSW.5.1. Illustration of study design.

6. A Priori Statistical Methods

6.1. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who give informed consent
Enrolled	All participants who continue the study after Visit 2.
Treated	All enrolled participants who receive at least 1 dose of the assigned IP after Visit 4

Abbreviations: IP = investigational product.

6.2. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of data will be conducted as deemed appropriate.

Efficacy analyses will be conducted on the treated population, including data collected prior to permanent discontinuation of IP. When change from baseline is included as a *response variable of analysis models*, the participant will be included in the analysis only if a baseline and a postbaseline measurement are available.

Safety analyses will be conducted on the treated population. Analyses of adverse events (AEs) and severe hypoglycemia will include data collected during the treatment period and baseline period. Adverse events during the follow-up period will be listed.

Unless otherwise noted, all tests will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (Cis) will be calculated at 95%, 2-sided. A gatekeeper method (Westfall and Krishen 2001) will be used to control the overall type 1 error for the primary and gated secondary objectives.

Baseline is defined as the last nonmissing measurement at or before Visit 4 unless otherwise specified.

A restricted-maximum-likelihood-based, mixed model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint of change from baseline in time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during daytime period will include the fixed class effect of visit, the covariate of baseline, and the random effect of participant. An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on least-squares means and Type III tests. SAS® PROC MIXED will be used to perform the

analysis. If this analysis fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- autoregressive with heterogeneity
- compound symmetry with heterogeneous variances
- Toeplitz
- autoregressive
- compound symmetry without heterogeneous variances

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

An analysis of covariance (ANCOVA) will also be used to analyze continuous variables collected only at baseline and endpoint. The model will include baseline as a covariate. Unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward (LOCF) approach, using only postbaseline data.

For continuous measures, summary statistics will include sample size, mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. Least-square means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements.

For categorical measures, summary statistics will include sample size, frequency, and percentages.

Table ITSW.6.1. Baseline and Post-Baseline Definitions and Patient Population by Type of Analysis

Analysis	Patient Population	Baseline Observations	Post-Baseline Observations
HbA1c MMRM	All treated patients with a baseline and at least one post-baseline observation	Last of Visits 1-4	Visits 7, 9, and 12 prior to discontinuation of IP
HbA1c categorical analysis longitudinal logistic regression	All treated patients with a baseline and at least one post-baseline observation	Last of Visits 1-4	Visits 7, 9, and 12 prior to discontinuation of IP
CGM outcomes	All treated patients with a baseline and at least one post-baseline observation	Visit 4	Visits 7, 9, and 12 prior to discontinuation of IP
Basal, bolus, and total insulin doses, and bolus/total insulin dose	All treated patients with a baseline and at least one	Visit 4	Visits 6, 7, 9, and 12 prior to discontinuation of IP

ratios continuous analysis	post-baseline observation		
Health outcomes: ITSQ, DSAT	All treated patients with a baseline and a post-baseline observation	Last of Visits 2-4	Visit 12 prior to discontinuation of IP
Health outcome: Study mealtime insulin experience question	All treated patients with a post-baseline observation	NA	Visit 12 prior to discontinuation of IP
Weight and vital signs	All treated patients with a baseline and at least one post-baseline observation	Last of Visits 1-4	Visits 7, 9, and 12 prior to discontinuation of IP
Severe Hypoglycemia events	All treated patients	The entire baseline period	The entire treatment period
TEAEs	All treated patients	From Visit 2 to the first dose of assigned IP	From first dose of assigned IP to last dose of assigned IP Follow up period
Postprandial incremental AUCs	All treated patients with a baseline and a post-baseline observation	Visit 4	Visit 12 prior to discontinuation of IP

6.3. Patient Disposition

Patient disposition will be displayed in a flowchart showing the number of patients entered, enrolled, treated, and discontinued across all study periods.

Frequency counts and percentages of all treated patients completing and discontinuing from the study will be presented. Reasons for discontinuation from the study and study treatment will be summarized.

Frequency counts and percentages of all patients entered, enrolled, and discontinued from the study during the baseline period will be summarized. Reasons for discontinuation during screening will be summarized for all entered patients. Reasons for discontinuation during the baseline period will be summarized for all enrolled patients.

A listing of the primary reason for treatment discontinuation (if applicable) and study discontinuation will be generated for the treated population.

Patient allocation by investigator will be summarized indicating the number of patients who enter the study, the number of patients who participate in the baseline period, the number of

patients treated, and the number of patients who discontinue the study during the 12-Week treatment period.

6.4. Patient Characteristics

A summary table will be generated for patient and diabetes characteristics at study entry using all treated patients. The following variables will be included but not limited to: age, age groups (<65, ≥65 years), sex, ethnicity, race, height, weight, body mass index (BMI), BMI group (<25, ≥25 to <30, ≥30 to <35, ≥35 kg/m2), duration of diabetes, participant's prior CGM use, Use of SGLT2, Use of injectable GLP-1, prandial dosing plan (carbohydrate counting/fixed dose), HbA1c at study entry and baseline.

For continuous variables, the following statistics will be provided: mean, SD, minimum, maximum, and median. For categorical variables, summary statistics will include sample size, frequency and percentage. A listing of patient characteristics at study entry will be provided.

For all treated patients, the number and percentage of patients with preexisting conditions will also be summarized using Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) nested within system organ class (SOC). Preexisting conditions are conditions that are still ongoing at inform consent. Events will be ordered by decreasing frequency.

6.5. Treatment Compliance

No analysis for treatment compliance is planned for this study.

6.6. Important Protocol Deviation

Important protocol deviations (IPD) that potentially compromise data integrity or patients' safety will be summarized for all treated patients. The listing of important protocol deviations for all treated patients during the entire study will be provided in the CSR. The IPDs identified by site monitoring and clinical database will be integrated in the listing. If the IPD is identified by both methods, only the site monitoring IPD will be presented.

6.7. Concomitant Therapy

Concomitant medication will be summarized for the treated population during the treatment periods (0 to 12 weeks). The percentages of patients receiving each concomitant medication will be summarized using PT nested within Anatomical Therapeutic Chemical (ATC) Level 3 code. Medications will be ordered by decreasing frequency within ATC level. Concomitant medication used during the baseline period will also be summarized for the enrolled population.

The daily basal dose, daily bolus dose, total insulin dose, and the ratio of bolus dose to total insulin dose during the baseline period will be summarized. The doses and bolus/total insulin dose ratios for each visit will be calculated as the mean of the doses for the last 3 days prior to the visit date that are entered in the electronic case report form (eCRF). Doses will be summarized in U and U/kg.

6.8. Efficacy Analyses

6.8.1. Primary Endpoint

The primary efficacy comparison will be based on the MMRM analysis of change from baseline in time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during daytime period including data collected prior to permanent discontinuation of IP. The analysis model and selection of covariance structure is described in Section 6.2.

6.8.2. Gated/Other Secondary Endpoints

The analysis of the secondary gated objectives will be conducted if the time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period at study endpoint versus baseline is found statistically significant for the primary efficacy analysis at a 2-sided 0.05 significance level (Westfall and Krishen 2001). If this contrast is significant, the secondary objectives were tested in sequence until the first null hypothesis in the sequence failed to be rejected at a 2-sided 0.05 significance level. The sequential testing for gated secondary objectives is conducted in the following order to assess whether value at study endpoint is superior to baseline:

1. To evaluate HbA1c
2. To evaluate time glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the 24-hour period.

For continuous longitudinal secondary endpoints, the MMRM model similar to that for the primary analysis will be used. Duration and percent time in range, time in hypoglycemia, and time in hyperglycemia derived from CGM data will also be analyzed using an MMRM model. Details for the CGM analyses can be found in Section 6.10.

Continuous nonlongitudinal secondary endpoints will be analyzed using the ANCOVA. Postprandial incremental area under the curve $(AUC)_{0\text{-}1\ hour}$ and incremental $AUC_{0\text{-}2\ hour}$ will be analyzed by ANCOVA described in Section 6.2.

Proportion of participants with HbA1c <7.0% and ≤6.5% will be analyzed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model with the fixed class effect of visit, the covariate of baseline HbA1c, and the random effect of participant.

Actual and change from baseline in basal, bolus, and total dose, as well as the bolus/total insulin dose ratio will be analyzed by the MMRM models described in Section 6.2.

6.8.3. Analyses of Exploratory Efficacy and Health Outcomes Objectives

Proportion of patients who have achieved the below recommended individual and composite CGM targets (Battelino 2019) of glycemic control at Visit 12 (10 - 12 weeks) will be summarized:

- percentage of time in target CGM glucose range (70-180 mg/dL [3.9-10.0 mmol/L]) >70%

- percentage of time in hypoglycemia (<54 mg/dL [<3.0 mmol/L]) <1%
- percentage of time in hyperglycemia (>250 mg/dL [>13.9 mmol/L]) <5%

In addition, proportion of patients who have achieved the below recommended individual CGM targets of glycemic control at Visit 12 (10 - 12 weeks) will be summarized:

- percentage of time in hypoglycemia (<70 mg/dL [<3.0 mmol/L]) <4%
- percentage of time in hyperglycemia (>180 mg/dL [>13.9 mmol/L]) <25%

Average glucose for a 24-hour period from each 14-day CGM session at Visit 12 (10 - 12 weeks) and baseline (-2-0 weeks) will be analyzed by ANCOVA described in Section 6.2.

Within-day and between-day glycemic variability measured by the SD and the coefficient of variation (CV) of CGM data will also be analyzed by the ANCOVA model specified in Section 6.2. Details for the glycemic variability derivation can be found in Appendix 1.

In addition, CGM outcomes that are not included in the primary or secondary efficacy endpoints will be analyzed as exploratory efficacy endpoints. Details for the CGM analyses can be found in Section 6.10.

For the ITSQ, the change from baseline to LOCF endpoint while on treatment in each domain transformed score (inconvenience, lifestyle, hypoglycemic control, glycemic control, and delivery system) and overall transformed score will be analyzed using ANCOVA.

For the DSAT, the change from baseline to LOCF endpoint, while on treatment, in each item and a total score will be analyzed using ANCOVA.

Summary statistics, including number of participants and proportion of a categorical outcome (5 levels) for the study mealtime insulin experience question will be provided.

6.9. Safety Analyses

Safety measures will include AEs, severe hypoglycemia, vital signs and weight, and treatment exposure.

Continuous safety variables, as well as the change from baseline for these variables, will be analyzed either by MMRM or ANCOVA models. Categorical variables will be summarized unless otherwise specified.

6.9.1. Extent of Exposure

Duration of exposure to study drug will be summarized based upon eCRF data. The following summary statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (that is, total patient-years of exposure). The number and proportion of patients falling into the following different exposure categories will also be summarized: <4 weeks (>0 and <28 days), ≥4 and <8 weeks (≥28 and <56 days), ≥8 and <12 weeks (≥56 and <84 days) and ≥12 weeks (≥84 days).

Patients who complete the study treatment period are required to complete a safety follow-up visit without study drug. The days on study after discontinuing IP, and the days on study from date of first study drug to the last study visit date up to Visit 801 will also be summarized.

6.9.2. Adverse Events

Events that are newly reported after the first dose of IP or are reported to worsen in severity from baseline will be considered treatment-emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities (MedDRA) lowest-level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity.

Serious adverse events (SAEs), AEs reported as reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the MedDRA PT, sorted by decreasing frequency. Treatment-emergent adverse events will also be summarized by PT sorted by decreasing frequency within SOC for all TEAEs and by maximum severity. For events that are specific to only 1 sex, the denominator and computation of the percentage will include only participants from the given sex. The number and proportion of participants with at least 1 event for each type of event will be summarized.

6.9.3. Hypoglycemic Events

Only severe hypoglycemia will be collected as AEs and all episodes of severe hypoglycemia will be considered as SAEs. Severe hypoglycemia rates and incidence during the treatment period (Visits 4-12) will be summarized.

A listing of patients with at least 1 severe hypoglycemia reported (as SAE) after Visit 4 (including Visit 801) will be provided.

A list of MedDRA PTs will be used for the narrow search of potential severe hypoglycemia in spontaneously reported AEs. The events identified through the search strategy that are also reported as SAEs will be summarized.

6.9.4. Injection Site Reaction

Injection site reactions will be searched by MedDRA PTs from the spontaneous AE reporting of potential injection site reactions. The number and percentage of patients experiencing treatment-emergent injection site reaction AEs will be summarized.

6.9.5. Vital Signs and Other Physical Findings

Post-baseline measurements and change from baseline to post-baseline for vital signs and physical characteristics (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, weight, BMI) at the scheduled visits will be summarized for patients who have both baseline and at least 1 post-baseline result.

The measurements during the treatment period (0 to 12 weeks) will be analyzed by an MMRM model with baseline value of the response variable, visit as fixed factors and patient as the random factor.

6.9.6. Patient Narratives

Patient narratives will be provided for all patients in the study who experience any of the following "notable" events:

- deaths
- SAEs
- discontinuations from study (or study drug) due to AEs
- pregnancy

A list of patients who meet the criteria for narratives will be provided.

6.10. Continuous Glucose Monitoring Analysis

6.10.1. General Considerations

The analyses described in this section will include data collected during the entire baseline period and treatment period. Percentage and duration in target range, hypoglycemia, hyperglycemia will be analyzed for baseline (Week -2-0), Visit 7 (Week 2-4), Visit 9 (Week 6-8), and Visit 12 (Week 10-12). Other CGM variables will be analyzed for baseline (Week -2-0) and Visit 12 (Week 10-12).

To ensure that the CGM outcome variables are only calculated from CGM session days with sufficient data within the 24-hour, daytime (0600 hours to midnight), or nighttime (midnight to 0600 hours) periods, the following criterion will be used to determine a valid CGM session day to be counted into the calculation for a visit: minimum number of measures per day – at least 70% of the total measures that are supposed to be obtained (i.e., 70% of the 96 measures) for the 24-hour period.

6.10.2. CGM Variable and Analysis

The meal time will be collected in the database by eCRF. All continuous variables will be analyzed using the MMRM or ANCOVA defined in Section 6.2. LS mean of the difference between baseline (Week -2-0) and Visit 12 (Week 10-12) will be presented.

Summary statistics will include the number of observations, mean, median, maximum, minimum, and SD for all continuous measures. For categorical measures, the number of observations, proportion, and frequencies will be included in summary statistics. All analyses will be performed for data collected by visit.

Definition of the derived variables is in Appendix 1.

6.10.2.1. Target Glucose Range

- Percentage and Duration (in minutes) of time per day glucose values are within target range (defined as between 70 mg/dL and 180 mg/dL [3.9 and 10.0 mmol/L]) inclusive during the daytime period, nighttime period and 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within target range (defined as between 70 mg/dL and 140 mg/dL [3.9 and 7.7 mmol/L]) inclusive during the daytime period, nighttime period and 24-hour period.

6.10.2.2. Hypoglycemia

- Percentage and Duration (in minutes) of time per day where glucose values are within a hypoglycemic range (defined as<54 mg/dL [3.0 mmol/L]) during the daytime period, nighttime period and 24-hour period.
- Percentage and Duration (in minutes) of time per day where glucose values are within a hypoglycemic range (defined as <70 mg/dL [3.9 mmol/L]) during daytime period, nighttime period and 24 hour period.
- Percentage and Duration (in minutes) of time per day where glucose values are within a hypoglycemic range (defined as >=54 mg/dL [3.0 mmol/L] and <70 mg/dL [3.9 mmol/L]) during the daytime period, nighttime period and 24-hour period.

6.10.2.3. Hyperglycemia

- Percentage and Duration (in minutes) of time per day glucose values are within a hyperglycemic range (defined as >180 mg/dL [10.0 mmol/L] during daytime, nighttime and 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within a hyperglycemic range (defined as >180 mg/dL [10.0 mmol/L] and <=250 mg/dL [13.8 mmol/L]) during daytime, nighttime and 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within a hyperglycemic range (defined as >250 mg/dL [13.8 mmol/L]) during daytime, nighttime and 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within a hyperglycemic range (defined as >300 mg/dL [16.5 mmol/L]) during daytime, nighttime and 24-hour period.

6.10.2.4. Glycemic Variability

- Within-day and between-day glucose coefficient of variation during 24-hour period.
- Within-day and between-day glucose standard deviation during a 24-hour period.
- Overall glucose variability

6.10.2.5. Mean glucose

- Mean glucose value (mg/dl) during a 24-hour period

6.10.2.6. iAUC and mean postprandial sensor glucose excursions

iAUC and mean postprandial sensor glucose excursions:

- 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, 0 to 4 hours relative to meal starting time at the treatment level, excluding data collected after the next meal event
- 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, 0 to 4 hours relative to meal starting time by meal (breakfast, lunch, and dinner) at the treatment level, excluding data collected after the next meal event

6.10.2.7. Highest sensor glucose

Highest sensor glucose after meals:

- 0-4 hours relative to meal starting time at the treatment level, excluding data collected after the next meal event
- 0-4 hours relative to meal starting time by meal (breakfast, lunch and dinner) at the treatment level, excluding data collected after the next meal event

6.10.2.8. Target CGM glucose

- The proportion of participants with percentage of time in target CGM glucose range (70-180 mg/dL [3.9 and 10.0 mmol/L])>70%
- The proportion of participants with percentage of time in hypoglycemia (<54 mg/dl [3.0 mmol/L])< 1%
- The proportion of participants with percentage of time in hyperglycemia (>250 mg/dL [13.8 mmol/L])< 5%
- The proportion of participants with percentage of time in hypoglycemia (<70 mg/dl [3.9 mmol/L])< 4%
- The proportion of participants with percentage of time in hyperglycemia (>180 mg/dL [10.0 mmol/L])<25%

6.10.2.9. Other CGM variables

The following standardized glucose summary figures from the ambulatory glucose profile (AGP) will be generated, based upon the observed CGM data at baseline(week -2-0) and Visit 12 (Week 10-12):

- 24-hour period at individual patient level
- 24-hour period at the treatment level

Based upon the observed CGM data and patients dose time from study diary at baseline(week -2-0) and Visit 12 (Week 10-12):

- 0-4 hours relative to meal starting time at the treatment level, excluding data collected after the next meal event
- 0-4 hours relative to meal starting time by meal (breakfast, lunch and dinner) at the treatment level, excluding data collected after the next meal event

In addition, postprandial hypoglycemia during the following time interval after each meal and overall will also be derived:

- 0 to 1 hour, 0 to 2 hours, 2 to 4 hours, 0 to 4 hours relative to meal starting time at the treatment level, excluding data collected after the next meal event
- 0 to 1 hour, 0 to 2 hours, 2 to 4 hours, 0 to 4 hours relative to meal starting time by meal (breakfast, lunch, and dinner) at the treatment level, excluding data collected after the next meal event

6.11. Subgroup Analyses

The following subgroups will be analyzed using data collected prior to permanent discontinuation of IP to evaluate consistency of results on the primary efficacy measure if there are sufficient numbers of participants by subgroup (for example, 10%):

- age (<65 years, ≥65 years)

- baseline HbA1c (≤8%, >8%)
- participant's prior personal CGM use (yes/no)
- participant's SGLT2 use (yes/no)
- participant's injectable GLP-1 use (yes/no)
- prandial dosing plan (carbohydrate counting, fixed dose)
- sex (male or female)
- BMI (<30, ≥30; <35, ≥35 kg/m^2)
- duration of diabetes (using the median as the cutoff)
- race
- ethnicity

Analyses for primary efficacy measure will be performed using an MMRM model that includes the same fixed effect and covariate given for the primary analysis model plus factors of subgroup and 2-way interaction of subgroup and visit. The effect of subgroup at the primary endpoint (Week 12) will be evaluated to assess subgroup effect.

Additional subgroup analyses may also be performed.

6.12. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

6.13. Data Monitoring Committee (DMC)

No DMC is planned for this study.

7. References

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8. Appendices

Appendix 1. Derivation of CGM Variables

General Derivation Specifications

All CGM variables will be derived for each patient, for each valid CGM day and also overall for baseline (Week -2-0), Visit 7 (Week 2-4), Visit 9 (Week 6-8), and Visit 12 (Week 10-12).

No missing CGM values will be imputed.

Since the CGM values may not be measured at the exact same time for each day for a specific individual patient, due to device changes or gaps in usage, non-overlapping intervals ('buckets') of 15 minutes over 00:00:00 to 23:59:59 (00:00:00 to 00:14:59, 00:15:00 to 00:29:59, etc.) will be used for any derivations requiring time-matched measurements across days within a visit.

All CGM glucose derivations will be conducted in units of mg/dL and will be converted to mmol/L by multiplying by 0.0555.

Only readings from valid CGM days (defined in Section 6.10.1) collected during the entire baseline period and treatment period will be included in derivations, excluding data (if any) that are collected while patients temporarily are off study treatment.

Glucose in Target Ranges, Hypoglycemia- or Hyperglycemia

The percentage of time within a glucose range (target, hypo- or hyperglycemia ranges) will be calculated as the number of observations within the specified range divided by the number of observations in the time interval (e.g., 24-hour period). The duration (in minutes) within the glucose range will then be calculated as the percentage of time within the glucose range times the length of the period (24 hours, 18 hours, for the periods of 24-hour or daytime respectively).

For example, if a patient had a total of 5 observations with glucose values **<70** mg/dL (3.9 mmol/L) out of a total of 90 observations recorded in a 24-hour period, the percentage of time spent in hypoglycemia during the 24-hour period for this patient will be calculated as 5/90 = 5.6%. The duration (in minutes) with hypoglycemia (glucose value **<70** mg/dL [3.9 mmol/L]) during this 24-hour period for this patient will be calculated as the percentage of time within the glucose range times the length of the period 1440 minutes (24 hours), (i.e., 5/90*1440 = 80 minutes).

Incremental Area under the Glucose Curve (iAUC)

iAUC0-T will be calculated as the average value of iAUC on all valid CGM days during that visit with sufficient data to calculate the iAUC0-T (Section 6.10.1). For each day, iAUC0-T will be calculated as the sum of areas of all individual trapezoids within the time frame according to the formula:

$$i\text{AUC}_{0-\text{T}} = \sum_{i=1}^{k} Ai = \sum_{i=1}^{k} \frac{(G_i - G_0) + (G_{i-1} - G_0)}{2} \boldsymbol{\Delta t_i}$$

where A_i is area of the respective trapezoid, G_i is glucose concentration at a particular time, G_0 is the starting glucose concentration before the start of the meal, is the time interval between consecutive CGM values, which should be always 15 minutes unless missing data occur, and k is the total number of intervals within the time frame 0-T, and T could be 1 hr, 2 hr, 3 hr or 4 hr. If the intermediate time points are missing, the next available time point will be used in calculating the trapezoid area. Also since it is possible that $G_i < G_0$ or $G_{i-1} < G_0$, A_i could also be negative.

G_0, the starting glucose concentration, will be calculated as the average of the CGM values in the time window [-29, 0] mins relative to the start of the meal (at most 2 CGM values); G_k, the last glucose concentration, is defined as the CGM values in the window [0, +14] minutes relative to the last time point of the time frame. For example, to calculate $iAUC_{0\text{-}2hr}$ after the start of breakfast, G_k will be the CGM values in the window [0, +14] minutes relative to the 2 hours after the start of breakfast. The derivation of each $iAUC_{0\text{-}T}$ will require that G_0 and G_k values are both available and will exclude data collected after the next meal event.

Mean Sensor Glucose Excursions

Mean sensor glucose excursions 0 to T hour(s) in a valid postmeal time interval will be calculated by averaging all excursion values within the time interval 0-T, excluding data collected after the next meal event, where excursions are defined as $G_i - G_0$ as defined in iAUC.

Glucose Variability

Glycemic variability will be evaluated using the notation below:

- i represents a time point within a time period (a 24-hour period, daytime or nighttime)
- n represents the number of time points within the time period
- k represents a day within a visit
- m represents number of days CGM is performed at a visit
- $BG_{k,i}$ represents the glucose value at time point i on day k

Within-Day Variability

For variables assessing within-day variability, first determine the variability within each day, then average across days within a visit.

Within-day glucose standard deviation (SD) (Hirsch 2005; Rodbard 2009):

$$SD = \frac{1}{m}\sum_{k=1}^{m} \mathrm{SD}_k = \frac{1}{m}\sum_{k=1}^{m} \sqrt{\frac{\sum_{i=1}^{n} (\mathrm{BG}_{k,i} - \left\{\frac{\sum_{i=1}^{n} \mathrm{BG}_{k,i}}{\mathrm{n}}\right\})^2}{n-1}}$$

Within-day glucose coefficient of variation (CV) (Clarke 2009):

$$CV = \frac{1}{m}\sum_{k=1}^{m} CV_k = \frac{1}{m}\sum_{k=1}^{m} \frac{SD_k}{\left(\frac{\sum_{i=1}^{n} \mathrm{BG}_{k,i}}{\mathrm{n}}\right)} \times 100$$

Between-Day Variability

For variables assessing between-day variability, first determine the variability for each time points across days within a visit then average across all time points.

Between-day glucose standard deviation (SD) (Rodbard 2009):

$$SD = \frac{1}{m}\sum_{k=1}^{m} \mathrm{SD}_k = \frac{1}{m}\sum_{k=1}^{m} \sqrt{\frac{\sum_{i=1}^{n} (\mathrm{BG}_{k,i} - \left\{\frac{\sum_{i=1}^{n} \mathrm{BG}_{k,i}}{\mathrm{n}}\right\})^2}{n-1}}$$

Between-day glucose coefficient of variation (CV):

$$CV = \frac{1}{n}\sum_{i=1}^{n} CV_i = \frac{1}{n}\sum_{i=1}^{n} \frac{\mathrm{SD}_i}{\left(\frac{\sum_{k=1}^{m} \mathrm{BG}_{k,i}}{m}\right)} \times 100$$

In addition to the CGM outcomes above, SD and CV in the daily mean values will also be derived.

Overall Variability

The CV, SD will be calculated using the standard formulas across collected across all valid days for time interval in treatment period (Week 0-12).

Highest Postprandial Glucose

Highest postprandial glucose level excursions within 4 hours after meals, will be calculated as the maximum glucose value during 0 to 4 hours after start of meal, truncating the data at the next meal event.

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