Statistical Analysis Plan I8H-MC-BDCX (Version 3.0)

A Phase 3, Parallel-Design, Open-Label, Randomized Control Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Degludec in Insulin Naïve Adults With Type 2 Diabetes

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Title Page

Protocol Title: A Phase 3, Parallel-Design, Open-Label, Randomized Control Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Degludec in Insulin Naïve Adults with Type 2 Diabetes

Protocol Number: I8H-MC-BDCX (b)

Compound Number: LY3209590

Short Title: Efficacy and Safety of LY3209590 Compared to Degludec in Adults with Type 2 Diabetes Who Are Starting Basal Insulin for the First Time

Acronym: QWINT-2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

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Table of Contents

Version history

This Statistical Analysis Plan (SAP) for study I8H-MC-BDCX is the 3rd version and approved prior to the final database lock. The 1st version of the SAP was approved prior to the first participant visit. The SAP versions are based on the protocol, protocol amendment (a), and protocol amendment (b) approved on 04 Feb 2022, 15 Feb 2022, and 13 May 2022, respectively.

Table 1. SAP Version History Summary

Version	Section # and Name	Description of Change	Brief Rationale
Version 2, Jan 22, 2024	1.1. Objectives, Endpoints, and Estimands	Clarify the hypoglycemia endpoint included in the tertiary composite endpoints are level 2 or 3	For clarity
	2.1. Multiplicity Adjustment	Add the details of type I error control strategy and graphic testing scheme	Add additional information for clarity
	3. Analysis Sets	For EAS2, update data cutoff for degludec arm	The change is based on PK profile
	3. Analysis Sets	CGM primary analysis population definition	For clarity
	4.1. General Considerations	Update the definitions of baseline and post-baseline observations for different analysis	For clarity and consistency with data collection
	4.3.3.and 4.4.1.3. Sensitivity Analysis	1. Update the two-way tipping point analysis in 4.3.3. 2. Add sensitivity analyses by including inadvertently enrolled participants for primary and key secondary efficacy analyses	To address regulatory feedback
	4.5.2. Tertiary Efficacy Endpoints	Use EAS1 for the binary outcome endpoints and update the analysis details.	To address regulatory feedback
	4.6. Safety Analyses	1. For laboratory analysis, removed shift analysis, Treatment emergent high/low and add elevated or low values meeting specified levels. 2. Use risk difference and 95% for safety categorical data analysis.	Per PSAP update
	4.6.3.1.2. Hypoglycemic Events Derived from CGM	Add analysis for CGM-based hypoglycemic events	Per CGM international consensus statement 2023
	4.7.1. Immunogenicity	Simplified the section and reduced analysis at the study level	Per PSAP update

Version	Section # and Name	Description of Change	Brief Rationale
	6.6. Appendix 6: Derivation of CGM Variables	Update the definition for CGM-based hypoglycemia and other updates	Per CGM international consensus statement 2023
	6.13. Appendix 13: Statistical Analysis for China and all ME2 related sections	Remove all contents related to ME2	No extended enrollment into ME2 cohort is needed for any country in order to meet the regulatory requirement.
	Throughout SAP	Minor changes and reorganization	For clarity, no change to analysis methodologies, so not detailed
Version 3, Apr 2024	4.1.General Consideration; 4.4.2.1. Other Efficacy endpoints; 2. Tertiary Efficacy Endpoints; 4.5.2. Tertiary Efficacy Endpoints	Added treatment regimen analysis for the selected secondary and tertiary endpoints (fasting serum glucose, fasting glucose from SMBG, and selected CGM parameters);	To implement FDA's feedback for BDCV's SAP
	4.4.1. Key Secondary Endpoints	Added missing data at baseline will be imputed using MI approach under MAR assumption	Addition
	4.5.2. Tertiary Efficacy Endpoints	Modified missing data handling approach for hypoglycemia in the composite endpoints of HbA1c and hypoglycemia	To implement FDA's feedback for BDCV's SAP
	4.6.3.1.1. Participant-Reported Hypoglycemic Events	Added a sensitivity analysis that considers all hypoglycemic events as one hypoglycemic event until a succeeding glucose value is ≥ 70 mg/dL	To implement FDA's feedback for BDCV's SAP
	4.6.4. Device Product Complaints	Added analysis for device product complaints	According to the new SAP template requirement
	4.7.2. Subgroup Analyses	Updated the subgroups for race	To implement FDA's feedback for BDCV's SAP
	Appendix 6. Derivation of CGM Variables	Clarified definitions of valid CGM period and session; Added sensitivity analysis for selected CGM parameters that derived from all data.	To implement FDA's feedback for BDCV's SAP

1. Introduction

The study protocol contains a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. There are no changes to the analyses described in the protocol. This SAP includes the analyses details for efficacy, safety measures, patient-reported outcomes, and parameters based on continuous glucose-monitoring (CGM). Pharmacokinetic/pharmacodynamics (PK/PD) analyses will be conducted by the PK/PD group and will be described in the PK analysis plan. The specifications for tables, figures and listings will be described in separate documents.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
Demonstrate noninferiority of LY3209590 compared to insulin degludec for the treatment of T2D in adults	Change in HbA1c from baseline to Week 52
Key Secondary (Multiplicity Adjusted)	
Demonstrate noninferiority of LY3209590 compared to insulin degludec for participants using GLP-1 receptor agonists	Change in HbA1c from baseline to Week 52
Demonstrate noninferiority of LY3209590 compared to insulin degludec for participants not using GLP-1 receptor agonists	Change in HbA1c from baseline to Week 52
Demonstrate superiority of LY3209590 compared to insulin degludec in selected parameters of glycemic control	• Change in HbA1c from baseline to Week 52 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, collected during the CGM session prior to Week 52
Other Secondary	
Compare the effect of LY3209590 to insulin degludec in parameters of glycemic control	• Change from baseline to Week 26 of HbA1c • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, collected during the CGM session prior to Week 26 • Change from baseline to Week 26 and Week 52 of fasting glucose measured by SMBG • Glucose variability measured during the CGM session prior to Weeks 26 and 52 • Insulin dose at Weeks 26 and 52
Compare the effect of LY3209590 to insulin degludec on safety endpoints	• Incidence and rate of composite of Level 2 and 3 hypoglycemia events during treatment period • Incidence and rate of composite of Level 2 and 3 nocturnal hypoglycemia events during treatment period • Change from baseline to Weeks 26 and 52 in body weight • Measurements collected during CGM sessions prior to Weeks 12, 26, and 52 of

Objectives	Endpoints
	○ Time in hypoglycemia with glucose <70 mg/dL (3.9 mmol/L) ○ Time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L) ○ Time in hyperglycemia defined as glucose >180 mg/dL (10.0 mmol/L)
Compare the effect of LY3209590 to insulin degludec on patient-reported outcomes questionnaires	• Change from baseline to Weeks 26 and 52 of ○ TRIM-D ○ SF-36, and ○ EQ-5D-5L
Tertiary	
Compare the effect of LY3209590 to insulin degludec in participants using GLP-1 receptor agonists versus participants not using GLP-1 receptor agonists	• Rate of Level 1 and composite of Level 2 and 3 hypoglycemia events during the treatment period • Change from baseline to Weeks 26 and 52 in body weight • Insulin dose at Weeks 26 and 52 • Measurements collected during CGM sessions prior to Weeks 12, 26, and 52 of ○ Time in hypoglycemia with glucose <70 mg/dL (3.9 mmol/L) ○ Time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L) ○ Time in hyperglycemia defined as glucose >180 mg/dL (10.0 mmol/L), and ○ Time in glucose range between 70 and 180 mg/dL (3.9 mmol/L and 10.0 mmol/L), inclusive
Compare the effect of LY3209590 to insulin degludec for efficacy parameters	• Percentage of participants at Week 52 achieving ○ HbA1c <7% ○ HbA1c <7% without Level 2 or 3 nocturnal hypoglycemia, and ○ HbA1c ≤6.5% without Level 2 or 3 hypoglycemia • Change from baseline to Weeks 26 and 52 of fasting serum glucose
Compare the effect of LY3209590 to insulin degludec for safety parameters	• Incidence and rate of Level 2 hypoglycemia events during treatment period • Incidence and rate of Level 3 hypoglycemia events during treatment period • Evaluation of immunogenicity- incidence of positive LY3209590 treatment-emergent anti-drug antibodies
Characterize the PK/PD of LY3209590	• LY3209590 PK and concentration-response relationships to key safety and efficacy measures
Compare the effect of LY3209590 to insulin degludec for patient-reported outcomes	• SIM-Q and • Frequency of responses to Basal Insulin Experience of "likelihood of incorporating into routine"

Abbreviations: CGM = continuous glucose monitoring; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; SMBG = self-monitoring of blood glucose; SF-36 = Short Form-36 Version 2 Health Survey Acute Form; SIM-Q = Simplicity Questionnaire; T2D = type 2 diabetes; TRIM-D = Treatment-Related Impact Measure – Diabetes.

Primary estimand (for primary objective)

United States registration

The primary clinical question of interest is: "What is the treatment difference between LY3209590 and insulin degludec in HbA1c change from baseline after 52 weeks of treatment, in study eligible participants, regardless of treatment discontinuation for any reason and regardless of initiation of rescue medication?"

The *treatment regimen estimand* will be used for the primary objective and the attributes are described in the following table.

Treatment Regimen Estimand Attribute	Description
Population	Targeted study population. See Section 3 for details,
Endpoint	HbA1c change from baseline to Week 52.
Remaining intercurrent events	None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both addressed by the treatment condition of interest attribute.
Treatment condition	The randomized treatment regardless of treatment discontinuation and use of rescue medications.
Population-level summary	Difference in mean changes between treatment conditions.

Abbreviations: HbA1c = Hemoglobin A1c.

Rationale for estimand: the treatment regimen estimand estimates how participants with T2D are treated in clinical practice and considers both efficacy and safety.

Registration for countries outside the United States

The primary clinical question of interest is: "What is the treatment difference between LY3209590 and insulin degludec in HbA1c change from baseline after 52 weeks of treatment, in study eligible participants who adhere to the randomized treatment without intercurrent events during the study treatment period?"

The *efficacy estimand* will be used for the primary objective. This table describes the efficacy estimand attributes.

Efficacy Regimen Estimand Attribute	Description
Population	Targeted study population. See Section 3 for details.
Endpoint	HbA1c change from baseline to Week 52.
Remaining intercurrent events	None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both handled by the hypothetical strategy, for example, the potential outcome for those participants if the intercurrent events have not occurred will be estimated.
Treatment condition	The randomized treatment.
Population-level summary	Difference in mean changes between treatment conditions.

Abbreviations: HbA1c = Hemoglobin A1c.

Rationale for estimand: the efficacy estimand supports the interpretation of the treatment effect as participants adhere to study treatment and free from the confounding effect of rescue medications.

Secondary estimands (for multiplicity-adjusted objectives)

The superiority test in change from baseline to Week 52 (Visit 31) in HbA1c will also be based on the primary estimand described above.

The change from baseline to Week 52 (Visit 31) in HbA1c in the subpopulations of participants using or not using GLP-1 receptor agonists will use treatment regimen estimand for US registration and efficacy estimand for other countries.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured during CGM session prior to Week 52 (Visit 31) will use treatment regimen estimated for US registration and efficacy estimand for other countries.

1.2. Study Design

- This is a Phase 3, parallel-design, open-label, randomized control study to evaluate the efficacy and safety of LY3209590 administered once-weekly compared to insulin degludec administered daily.
- The study includes a 3-week screening and lead-in period, a 52-week treatment period, and a safety follow-up period approximately 5 weeks after the last visit in the treatment period.
- Assignment to treatment groups will be determined by an interactive web-response system (IWRS). Participants will be randomly assigned to 1 of the 2 treatment groups in 1:1 ratio (LY3209590: insulin degludec) at Visit 3 (Week 0). The number of participants in each subpopulation of participants using or not using GLP-1 RA will be approximately 50% of the study population with balanced treatment assignment. Stratification will be by country, HbA1c stratum at Visit 1 (Week -3) (<8.0%, ≥8.0%), sulfonylurea use at randomization, and GLP-1 RA use at randomization, regardless of oral or injectable administration.
- Rescue therapy will be considered during the treatment period if the participants meet the protocol criteria of severe, persistent hyperglycemia.
- If study intervention is permanently discontinued, the participant will be encouraged to continue participation in the study for continued monitoring. Both efficacy (including HbA1c) and safety data will continue to be collected per the schedule of activities in the protocol.
- Participants will collect blinded CGM for 2 weeks prior to Visit 3 (Week 0), for 4 weeks prior to Visit 7 (Week 4), Visit 15 (Week 12), Visit 24 (Week 26), Visit 31 (Week 52), and for 4 weeks after Visit 31 (Week 52). Dexcom G6 system provides readings every 5 minutes. In China, instead of the Dexcom G6 system, the Libre Freestyle H system which provides readings every 15 minutes will be used. Main analyses for CGM measurements will be conducted based on data from the Dexcom G6 system.

2. Statistical Hypotheses

Primary Hypothesis

The primary objective of this study is to test the hypothesis that LY3209590 is not inferior to insulin degludec on glycemic control as measured by change in HbA1c from baseline to Week 52 (Visit 31) in participants with T2D who are starting basal insulin for the first time. The null hypothesis (H_0) is the difference between LY3209590 versus insulin degludec in the change from baseline to Week 52 (Visit 31) in HbA1c is greater than the noninferiority margin (NIM). The 2-sided 95% confidence interval (CI) will be used for testing the noninferiority.

Secondary Hypotheses

The key secondary objectives (multiplicity adjusted) are to test the hypotheses that LY3209590 is:

- not inferior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31) for the subpopulation of participants using GLP-1 receptor agonists
  H_0: the difference (LY3209590-insulin degludec) >0.4%;
- not inferior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31) for the subpopulation of participants not using GLP-1 receptor agonists
  H_0: the difference (LY3209590-insulin degludec) >0.4%;
- superior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31)
  H_0: the difference (LY3209590-insulin degludec) ≥0.0;
- superior to insulin degludec with respect to time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, collected during the CGM collected session prior to Week 52 (Visit 31)
  H_0: the difference (LY3209590-insulin degludec) ≤0.0.

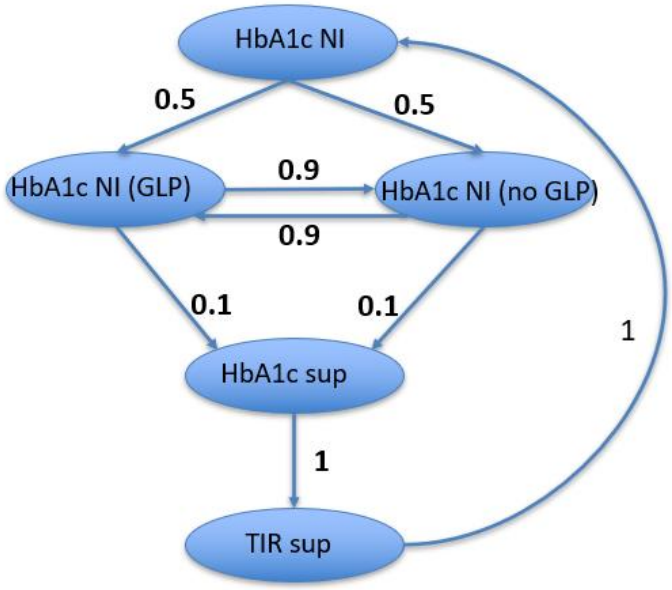
These hypotheses and the primary hypothesis will be tested using a strategy to control the overall Type 1 error.

2.1. Multiplicity Adjustment

A graphical approach (Bretz et al. 2009; 2011) for multiple comparisons will be used to ensure the strong control of the overall type I error rate for testing the primary and key secondary (multiplicity adjusted) objectives. The overall significance level (α) will be set to 0.05. The total α will be used for the primary objective first, then the α will be allocated and transitioned to other key secondary objectives once the primary objective is met. Therefore, the noninferiority test for the primary objective will be based on the 2-sided 95% CI. Once the upper limit of the 2-sided 95% CI is below the NIM, the non-inferiority is achieved and the α of 0.05 will be distributed to conduct the tests for the key secondary objectives. If the p-value of the 2-sided test for one of the key secondary objectives is below the assigned α level, the objective is demonstrated and the assigned α level will be distributed to the remaining objectives. The iterative test procedure continues until none of the remaining objectives can be demonstrated with their preserved α or all objectives are demonstrated successfully. The NIM of 0.4% (for treatment regimen estimand) and 0.3% (for efficacy estimand) will both be tested to meet different regulatory requirements. No multiplicity adjustments will be made for conducting

separate analyses relative to the efficacy and treatment regimen estimands. Each estimand will have its own familywise error rate of 0.05.

For primary and key secondary efficacy objectives, the details of type I error control strategy are illustrated in Figure 2.1. No multiplicity adjustments will be made for evaluating other secondary and exploratory objectives, or for safety assessments.



Primary: Change in HbA1c from baseline to Week 52 (LY3209590 noninferior to insulin degludec)

Key secondaries:
Change in HbA1c from baseline to Week 52
- for participants using GLP-1 RA;
- for participants not using GLP-1 RA;
(LY3209590 noninferior to insulin degludec)

Key Secondary: Change in HbA1c from baseline to Week 52 (LY3209590 superior to insulin degludec)

Key Secondary: Time in glucose range between 70 and 180 mg/dL 93.9 and 10.0 mmol/L), inclusive, collected during the CGM session prior to Week 52 (LY3209590 superior to insulin degludec)

Abbreviations: GLP-1 RA = glucagon-like peptide-1 receptor agonists; HbA1c= hemoglobin A1c; NI = noninferiority; sup = superiority.

Figure 2.1. Type 1 error control strategy for primary and key secondary efficacy endpoints.

3. Analysis Sets

The following analysis populations and data sets are defined for the purpose of analysis.

Analysis Populations/ Data Sets	Description
Entered Population	All participants who sign the informed consent form.
Randomized Population	All randomized participants. Participants will be analyzed according to the treatment they were assigned.
Modified Intent-to-Treat (mITT) Population	All randomized participants who took at least 1 dose of study treatment. Participants will be analyzed according to the treatment they were assigned.
Efficacy Analysis Set 1 (EAS1) for treatment regimen estimand on efficacy measures	The data will include: • mITT Population excluding participants discontinuing the study treatment due to inadvertent enrollment; and • all measurements regardless of the use of study treatment or rescue medications.
Efficacy Analysis Set 2 (EAS2) for efficacy estimand on efficacy measures	The data will include: • mITT Population excluding participants discontinuing the study treatment due to inadvertent enrollment; and • measurement up to the early discontinuation of study treatment or the initiation of rescue medication. The data cutoff for participants who had intercurrent events is defined by the earliest date from below dates for individual participants except for the analysis on study dose: • the date of last study dose + 10 days for LY3209590, or +1 day for degludec; and • the start date of the first rescue medication. The data cutoff for analysis on study dose is defined by the earliest date from below dates for individual participants: • the date of last study dose; and • the start date of the first rescue medication
Safety Analysis Set (SS)	The data will include: • mITT Population; and • all measurement regardless of the use of study treatment or rescue medications
Continuous Glucose Monitoring (CGM) Primary Analysis Population	All randomized participants who use Dexcom G6 system for CGM data collection.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designees. 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 changes to the data analysis methods described in the protocol, and the justification for making the change, will be described in this SAP or the clinical study report. Additional exploratory analyses of data will be conducted as deemed appropriate.

Unless otherwise stated, the efficacy analyses will be conducted on either EAS1 or EAS2. For treatment regimen estimand, efficacy analysis set 1 (EAS1 see the definition in Section 4) will be used; for efficacy estimand, other secondary and tertiary efficacy measures will be analyzed using the data up to the intercurrent events (EAS2 see the definition in Section 5). The treatment comparison will be based on either 2-sided test or 95% CI.

Unless otherwise noted, the safety analyses will be conducted on the SS. Percentages will be calculated using the safety population as the denominator. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex.

Unless otherwise stated, CGM analyses will be conducted based on the CGM Primary Analyses Population.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. For certain variables that are considered to be log-normally distributed, the geometric mean and coefficient of variation (CV) will be provided instead. Either the mixed model repeated measurement (MMRM) model or the analysis of covariance (ANCOVA) model will be used to analyze continuous outcomes. Least-squares (LS) means and standard errors derived from the analysis models will also be displayed. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons. For certain safety laboratory measures, log-transformed values will be analyzed in the statistical model instead. The actual change from baseline and percentage change from baseline will be presented using the derivation based on the output from the statistical model and the assumption of log-normality.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test or logistic regression will be used for treatment comparisons, unless otherwise stated. For laboratory values, both conventional (CN) and System International (SI) units will be presented. Therefore, both % and mmol/mol will be presented for HbA1c and both mg/dL and mmol/L will be presented for glucose measurements.

In this study, the negative binomial regression will be used to analyze the number of hypoglycemic episodes. Group Mean instead of LS mean will be estimated and delta method will be used to estimate the standard error of the Group Mean (Qu and Luo 2015). Group Mean is defined as the mean response in the treatment group for the studied population. The difference between LS mean and the Group Mean is that LS mean estimates the response by taking the

inverse link function on mean covariates, while the Group Mean takes the inverse link function on individual patient covariates first and then averages over all patients. For Level 2 hypoglycemia and severe hypoglycemia, the empirical method based on exposure adjusted rate (calculated by total number of events divided by total exposure) may be used for the treatment comparison if the number of episodes is too small and leads to convergency issues in the negative binomial regression model.

Below table describes the definition of baseline and post-baseline observations for different analyses.

Analysis	Baseline Observations	Post-Baseline Observations
HbA1c (treatment regimen estimand)	The baseline is the last non-missing assessment prior to or at the first day of study treatment.	Planned measurements at Visit 24 (secondary endpoint, Week 26) and Visit 31 (primary endpoint, Week 52) in EAS1. Use unplanned measurements if no planned measurement. Multiple imputation approach will be used to impute missing observations at Visit 24 (Week 26) and Visit 31 (Week 52).
HbA1c (efficacy estimand)	The baseline is the last non-missing assessment prior to or at the first day of study treatment.	Visit 5, 7, 15, 17, 24, 27, and 31 (Weeks 2, 4, 12, 16, 26, 36, and 52) in EAS2 for MMRM. Planned measurements at scheduled visits will be included. Use unplanned measurements if no planned measurements.
CGM parameters (treatment regimen estimand)	The baseline will be derived from the data collected during CGM session prior to the first dose date of study treatment. Multiple imputation will be used to impute missing observations at baseline.	The CGM session prior to Visit 24 (Week 26) and Visit 31 (Week 52) in EAS1 Multiple imputation approach will be used to impute missing observations at Visit 24 (Week 26) and Visit 31 (Week 52).
CGM parameters (efficacy estimand)	The baseline will be derived from the data collected during CGM session prior to the first dose date of study treatment.	The CGM sessions prior to Visit 7, 15, 24, and 31 (Weeks 4, 12, 26, and 52) in EAS2 for MMRM

Analysis	Baseline Observations	Post-Baseline Observations
Insulin dose during the treatment period	N/A	All scheduled visits between Visit 3 and Visit 31 in EAS2 for MMRM. The averages of **weekly** basal insulin doses between visits for individual participants will be used in the analysis. (Section 4.4.2.1)
Fasting glucose by SMBG	The baseline period is the lead-in period up to the day of first dose of study treatment. Baseline will be derived as the average of all fasting glucose measurements between V2 date and the first dose date. Multiple imputation will be used to impute missing observations at baseline for treatment regimen estimand.	All available data after the day of first dose of study treatment up to Week 52 (Visit 31) in EAS2 for MMRM (efficacy estimand). Values at each visit will be derived as average of all fasting glucose measurements from the day post prior visit up to the day of next visit. Data at Week 26 (Visit 24) and Week 52 (Visit 31) in EAS1 for ANCOVA with multiple imputation for missing data (treatment regimen estimand).
Fasting serum glucose	The baseline is the last non-missing assessment prior to or on the day of the first dose of study treatment. Multiple imputation will be used to impute missing observations at baseline for treatment regimen estimand.	All scheduled visits after the day of first dose up to Week 52 (Visit 31) in EAS2 for MMRM (efficacy estimand) Planned measurements at scheduled visits will be included. Data at Week 26 (Visit 24) and Week 52 (Visit 31) in EAS1 for ANCOVA with multiple imputation for missing data (treatment regimen estimand) .

Analysis	Baseline Observations	Post-Baseline Observations
Participant-reported hypoglycemia	The baseline period is the lead-in period prior to the first dose date of study treatment.	• Treatment period starts on the first dose date of study treatment and ends o At Week 52 (Visit 31) if completed treatment o on the last dose date of study treatment + 10 days for LY3209590, +1 day for degludec if discontinued study treatment early • Post-treatment period starts from o Week 52 (Visit 31) +1 day if completed treatment o last dose date of treatment +11 days for LY3209590, +2 days for degludec if discontinued study treatment early and ends on the last date in the study
TEAEs	The baseline period includes the screening/lead-in period up to the first dose of study treatment (The AE Start Relative to Exposure Assessment CRF is used to determine).	Safety analysis period starts after the first dose and ends at the last visit in the study including safety follow-up period.
Safety laboratory tests, vital signs, and body weight	The baseline will be the last non-missing assessment prior to or on the first dose date of study treatment Planned measurements at scheduled visits will be included.	• All scheduled visits after the first dose date up to Visit 802 for MMRM or ANCOVA Planned measurements at scheduled visits will be included.
laboratory values elevated or low, vital signs and body weight categorical measures	Starts from the screening visit and ends prior to or on the day of first dose of study treatment . All available measurements at scheduled and unscheduled visits will be included. The baseline for weight will be the last non-missing value during the baseline period.	Starts after the day of first dose of study treatment and ends at the last visit in the study including both treatment period and follow-up period. All available measurements at scheduled and unscheduled visits in the specified analysis period will be included.

Analysis	Baseline Observations	Post-Baseline Observations
Anti-LY3209590 antibody	Refer to PSAP	Refer to PSAP
Patient-reported outcomes	The baseline will be the data collected at Visit 3	• All scheduled visits after Visit 3 • Last collection after Visit 3

Abbreviation: ANCOVA = analysis of covariance; CGM = continuous glucose monitoring; CRF = case report form; EAS1 = efficacy analysis set 1; EAS2 = efficacy analysis set 2; MMRM = mixed model repeated measurement; N/A = not applicable; TEAE = treatment-emergent adverse event.

All analyses will be implemented using SAS Enterprise Guide Version 7.1 or above.

4.2. Participant Dispositions

Reasons for discontinuation prior to randomization including screen failure will be summarized for all participants who sign the informed consent form.

The number and percentage of participants who have completed/discontinued from the study/treatment will be summarized by treatment using the Randomized Population. The individual reasons for discontinuation will also be included in the summary. Comparison will be conducted using the Fisher's exact test.

A listing of the reasons for study/treatment discontinuations will be generated for the Randomized Population. A listing of the randomized treatment for this study will also be provided.

Time to permanent discontinuation of study treatment, time to study discontinuation and time to early discontinuation of study treatment due to AEs (if there is a sufficient number to warrant a summary) will be presented as a figure.

4.3. Primary Endpoint Analysis

4.3.1. Definition of endpoint(s)

The primary endpoint of this study is the HbA1c change from baseline to Week 52 (Visit 31). The HbA1c is reported in unit of % by central laboratory and will be converted to the unit of mmol/mol using the following formula: HbA1c in mmol/mol = 10.93 * HbA1c in % - 23.5 (http://www.ngsp.org/ifccngsp.asp). The HbA1c analysis will be conducted for both units.

4.3.2. Main analytical approach

The primary objective is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control in the targeted study population. The noninferiority test will be based on either of the 2 estimands: ***treatment regimen estimand*** for the US FDA submission and ***efficacy estimand*** for registrations in other countries. The full significance level of 0.05 will be used for each estimand.

The following table provides the details of treatment regimen estimand and efficacy estimand.

	Treatment Regimen Estimand	Efficacy Estimand
Analysis Population	All participants in EAS1 with non-missing baseline measure	All participants in EAS2 with non-missing baseline measure and at least one non-missing post-baseline scheduled measure
Analysis Data	All non-missing observations at baseline and Week 52 (Visit 31) regardless of the use of study intervention or rescue medications.	All non-missing observations at baseline and all scheduled post-baseline timepoints during treatment period (that is, Weeks 2, 4, 12, 16, 26, 36 and 52) (prior to the date of last study dose + 10 days for LY3209590 (+1 day for degludec), or the initiation of rescue medication whichever is earlier for participants with intercurrent events).
Missing Data	There may be missing values at Week 52 (Visit 31) due to early study discontinuation. The missing values will be imputed using multiple imputation by the retrieved dropout approach. The retrieved dropout participants are those who discontinue study intervention prior to Week 52 but have non-missing measures at Week 52 in the same treatment arm. If there are only a limited number of retrieved participants that leads to a failure in performing the multiple imputation analysis, such as the model cannot converge, or the number of retrieved dropout participants is small (i.e., at least 1 arm has <8 participants who discontinued study treatment early and have endpoint visit measurements), the missing HbA1c at Week 52 will be imputed by return-to-baseline multiple imputation approach (Qu and Dai 2022)	There may be missing values due to the early discontinuation of study intervention or use of rescue medication. The MMRM model will be used, and the missing values will be handled in the MMRM analysis under the assumption of missing at random.

	Treatment Regimen Estimand	Efficacy Estimand
Analysis Model	After the imputation, the observed and imputed data will be analyzed by the ANCOVA model using treatment, strata (country, GLP-1 RA treatment at randomization, and SU use at randomization), and baseline value of the dependent variable as independent variables. The statistical inference will be based on the multiple imputation framework by Rubin (1987).	The MMRM model will include treatment, strata (country, GLP-1 RA treatment at randomization, and SU use at randomization), visit and treatment-by-visit interaction as fixed effects, and baseline of the dependent variable as a covariate. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for the MMRM models. An unstructured covariance structure will be used to model the within-participant errors. If this structure fails to converge, the following covariance structures will be used in order until one converges: 1. Toeplitz with heterogeneity 2. autoregressive with heterogeneity 3. compound symmetry with heterogeneous variances 4. Toeplitz 5. Autoregressive 6. compound symmetry without heterogeneous variances.

Abbreviation: ANCOVA = analysis of covariance; MMRM = mixed model repeated measurement.

The 2-sided 95% CI of the LS mean difference (LY3209590 – insulin degludec) in the HbA1c change from baseline to Week 52 (Visit 31) will be estimated. For both estimands, LY3209590 will be declared noninferior to insulin degludec if the upper limit of the 2-side 95% CI for the LS mean difference in the HbA1c (measured in %) change from baseline is below NIM of +0.4%. In addition, the 95% CI for the LS mean difference will be compared to an alternative NIM of +0.3%.

4.3.3. Sensitivity Analysis

4.3.3.1. Two-way Tipping Point Analysis

To confirm the robustness of the primary endpoint results, a 2-way tipping point analysis that represents varying assumptions for missing data from both treatment groups will be conducted. This sensitivity analysis will focus on missing data at the primary endpoint. Penalty parameters for imputed missing values will be added for both treatment arms. The ANCOVA model for treatment regimen estimand will be conducted after penalty parameters are added. The multiple imputation framework by Rubin (1987) will be used to summarize the results.

The corresponding p-value of non-inferiority test will be shown by color scale in the figure.

Additionally, imputation under the noninferiority null hypothesis will be conducted by adding 0.4 (NIM) to the imputed data using treatment regimen estimand (Section 4.3.2) for the LY3209590

group only. The ANCOVA model for treatment regimen estimand will rerun using the adjusted data. The multiple imputation framework by Rubin (1987) will be used to summarize the results.

4.3.3.2. Including Inadvertently Enrolled Participants

The primary efficacy analysis will be repeated for both treatment regimen estimand and efficacy estimand by including inadvertent enrolled participants using mITT population.

4.3.4. Supplementary Analyses

Additional analysis may be conducted as needed.

4.4. Secondary Endpoints Analysis

4.4.1. Key Secondary Endpoints

A graphical approach (Figure 2.1) will be used to control the overall type I error for the primary objective and test LY3209590 is 1) not inferior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31) for the subpopulation of participants using GLP-1 receptor agonists; 2) not inferior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31) for the subpopulation of participants not using GLP-1 receptor agonists; 3) superior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31); 4) superior to insulin degludec with respect to time in glucose range between 70 and 180 mg/dL inclusive, collected during the CGM collected session prior to Week 52 (Visit 31).

4.4.1.1. Definition of endpoint(s)

See Section 4.3.1 for the HbA1c change from baseline to Week 52 (Visit 31).

The time in glucose range between 70 and 180 mg/dL inclusive will be based on the percentage of CGM readings within the glucose range during the specific CGM session. The derivation of CGM parameters is provided in Appendix 6 (Section 6.6).

4.4.1.2. Main analytical approach

The non-inferiority test in change from baseline to Week 52 (Visit 31) in HbA1c for each of the subpopulations with participants using or not using GLP-1 RA will be analyzed. For the treatment regimen estimand (using data from the EAS1), for each subpopulation, the missing data will be imputed by multiple imputation with the approach similar to the imputation used for the primary endpoint. The imputed data for that subpopulation will be analyzed by the ANCOVA model using treatment, strata (country and SU use at randomization), and baseline HbA1c as independent variables. For the efficacy estimand (using data from the EAS2), the MMRM model which includes treatment, strata (country and SU use at randomization), visit and treatment-by-visit interaction as fixed effects, and baseline HbA1c as a covariate will be used, with data from that subpopulation.

The superiority test in change from baseline to Week 52 (Visit 31) in HbA1c will be based on the same primary endpoint analysis described in Section 4.3.2.

The time in glucose range between 70 and 180 mg/dL inclusive measured by CGM will be analyzed using an ANCOVA model for treatment regimen estimand and an MMRM model for efficacy estimand. CGM Primary Analysis Population will be used for the analyses. The analyses are similar to the primary analysis described in Section 4.3.2 with additional term of baseline HbA1c stratum (<8.0%, ≥8.0%) in analysis models. For treatment regimen estimand, only participants with an observation at baseline or at Week 52 will be included in the analysis. the missing data at Week 52 will be imputed by multiple imputation with the approach similar to the imputation used for the primary endpoint. The missing baseline will be imputed using multiple imputation under assumption of missing at random.

4.4.1.3. Sensitivity Analysis

The analyses described in Section 4.4.1.2 will be repeated for both the treatment regimen estimand and efficacy estimand by including inadvertent enrolled participants using mITT population.

4.4.2. Supportive secondary Endpoint(s)

4.4.2.1. Other Efficacy Endpoints

The analysis of change from baseline for HbA1c at Week 26, fasting glucose by SMBG at Week 26 and 52, CGM (except for variability) parameters at Week 26 and 52 will be performed for both treatment regimen estimand and efficacy estimand. The analyses for other supportive efficacy endpoints will be based on the EAS2 data.

For treatment regimen estimand, only participants with an observation at baseline or at the endpoint visit will be included in the analysis. The missing baseline will be imputed using multiple imputation under assumption of missing at random. Missing data at the endpoint visit will be imputed using either retrieved dropout or return-to-baseline multiple imputation approach determined by the criterion described for the primary efficacy endpoint in Section 4.3.2. ANCOVA analysis will be conducted similar to that for the primary endpoint. An additional term of baseline HbA1c stratum (<8.0%, ≥8.0%) will be added into the model for the endpoints other than HbA1c.

For efficacy estimand, participants with baseline and at least one post baseline observation will be included in the analysis. The longitudinal observations of actual and change from baseline in HbA1c to Week 26 will be analyzed using the same MMRM model as for the efficacy estimand described in Section 4.3.2. The analyses of other continuous efficacy measures (fasting glucose, insulin dose and CGM parameters) will use an MMRM model similar to that for the primary endpoint with an additional term of baseline HbA1c stratum (<8.0%, ≥8.0%). The variance-covariance structure in the MMRM models for fasting glucose from SMBG and insulin dose will be based on compound symmetry.

Longitudinal logistic regression model with baseline value, strata (country, GLP-1 use at randomization, SU use at randomization and baseline HbA1c stratum [<8.0%, ≥8.0%]), Treatment, Time, and Treatment-by-time interaction as factors will be used for analysis for CGM targets of glycemic control. See Section 4.3.2 for variance-covariance structure selection.

The time point for primary CGM data analysis is CGM session. In addition, the average time in glucose range, hypoglycemia range and hyperglycemia range by week (by visit for treatment period) will be summarized by treatment. Average daily time within each range since last dose

by CGM Session during treatment period will also be summarized for LY3209590. Missing data patterns will be summarized at daily, weekly (visit) and CGM session levels.

For CGM parameters, data from participants in China using Libre Freestyle H system will be analyzed separately (Appendix 6 [Section 6.6]).

The analysis of study insulin dose will use an MMRM model on the EAS2 data with treatment, strata (country, GLP-1 RA treatment at randomization, SU use at randomization, and baseline HbA1c stratum [<8.0%, ≥8.0%]), visit and treatment-by-visit interaction as covariates. The average weekly dose during each visit for individual participants will be used in the analysis. In the LY3209590 group, the average dose of each visit (that is, average of weekly doses since last visit) will be used as the average weekly dose. In the insulin degludec group, the average weekly dose will be calculated by the average daily dose multiplying by 7. The analysis will be repeated for average daily dose in U and daily dose in U/kg. The body weight at the visit will be used to calculate the daily dose in U/kg at the same visit.

4.4.2.2. Other Safety Endpoints

The safety measures based on CGM data will be analyzed as described in Section 4.4.2.1. For other safety measures, the details are provided in Section 4.6.

4.4.2.3. Patient Reported Outcome

The analyses for patient-reported outcomes will be based on the EAS2 data.

4.4.2.3.1. Treatment-Related Impact Measure – Diabetes (TRIM-D)

The TRIM-D is a self-administered instrument, which assesses the impact of diabetes treatment on participants' functioning and well-being across available diabetes treatments (Brod et al. 2009). The TRIM-D consists of 28 items each assessed on a 5-point scale, where higher scores indicate a better health state, with a recall period of "over the past 2 weeks". In addition to an overall score, the TRIM-D items assess 5 domains of impact:

- Treatment Burden (6 items: Question 1a, Question 2a to 2e),
- Daily Life (5 items: Question 3a to 3b, Question 5a to 5c),
- Diabetes Management (5 items: Question 4a to 4e),
- Compliance (4 items: Question 6a, b, c, e), and
- Psychological Health (8 items: Question 6d, Question 7a to 7g)

Items within each domain are summed to obtain a raw domain score, which is then transformed to a scale of 0 to 100 to obtain a transformed domain score. The transformed domain score can be calculated by

$$\frac{(\text{sum of raw score - sum of lowest possible raw score})}{(\text{sum of highest possible raw score - sum of lowest possible raw score})} \times 100$$

For an example, Diabetes Management = ([sum of raw score -5]/[25-5])×100. If answer for the 5 questions in Diabetes Management (Question 4a to 4e) are all 1, then the sum of raw score is 5 and the transformed domain score is 0. All items can also be summed and transformed to obtain a transformed total score in a similar way.

Summary statistics for the transformed scores of each domain will be provided by study treatment. The scores at scheduled visits and the change from baseline will be analyzed by the MMRM model similar to the other efficacy endpoints (see Section 4.4.2.1). The last non-missing postbaseline observations will be analyzed by an ANCOVA model using the independent variables of treatment, strata (country, GLP-1 RA treatment at randomization, SU use at randomization, and baseline HbA1c stratum), and baseline value of the dependent variable as independent variables.

4.4.2.3.2. Short-Form-36 Health Survey Version 2, Acute Form

Per copyright owner, the QualityMetric Health Outcomes™ Scoring (PRO_CoRe V2.0) Software will be used to derive the following domains:

- Physical Functioning domain,
- Role-Physical domain,
- Bodily Pain domain,
- General Health domain,
- Vitality domain,
- Social Functioning domain,
- Role-Emotional domain, and
- Mental Health domain.

and component summary scores:

- Mental Component Score, and
- Physical Component Score.

Each domain is scored individually, and information from these 8 domains is further aggregated into 2 health component summary scores, the Physical Component Summary and Mental Component Summary. Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10. Higher scores indicate better levels of function and/or better health (Maruish 2011).

Summary statistics for the component summary scores and scores in each domain will be provided by study treatment. The scores at scheduled visits and the change from baseline will be analyzed by the MMRM model similar to the other efficacy endpoints (see Section 4.4.2.1) for the scheduled postbaseline visits and by the ANCOVA model similar to the TRIM-D for the last non-missing postbaseline observations.

4.4.2.3.3. EQ-5D-5L

The EQ-5D-5L (EuroQol Research Foundation 2019) is a standardized 5-item self-administered instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L assesses 5 dimensions of health:

- mobility,
- selfcare,
- usual activities,
- pain/discomfort, and
- anxiety/depression.

The 5L version, scores each dimension at 5 levels:

- no problems,
- slight problems,
- moderate problems,
- severe problems, and
- unable to perform/extreme problems.

In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health).

The second part of the questionnaire consists of EQ Visual Analog Scale (VAS) which records the respondent's self-rated health status. The participant rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health). In conjunction with the health state data, it provides a composite picture of the respondent's health status.

The frequency and proportion of each level for a given item will be summarized by study treatment for each scheduled visit. The EQ-5D-5L index, EQ VAS score and their change from baseline will be analyzed by the MMRM model similar to the other efficacy endpoints (see Section 4.4.2.1) for the scheduled postbaseline visits and by the ANCOVA model similar to the TRIM-D for the last non-missing postbaseline observations.

4.4.2.3.4. Simplicity Questionnaire (SIM-Q) Single Medication status version

The Simplicity of Diabetes Treatment Questionnaire (SIM-Q) single medication status version is a brief 10-item measure developed to assess the simplicity and complexity of treatment for T2D. This measure asks participants to think about a specific medication (prior basal insulin or current study treatment) when completing each item on a 5-point scale ranging from "Very complex" to "Very simple." In Study BDCX, only the last 2 questions of the SIM-Q will be completed – "How simple or complex is your medication treatment for diabetes?" and "Overall, how simple or complex is it to manage your diabetes, including medication, checking your blood glucose levels, diet, and any other aspects of diabetes treatment?"

The frequency and proportion of the response for each question will be summarized for each scheduled visit. Treatment comparison will be conducted by Wilcoxon rank sum test.

4.4.2.3.5. Basal Insulin Experience: Likelihood of incorporating into routine

This is a Lilly-developed, participant-completed question to understand the participant's likelihood of incorporating their study insulin into their diabetes management routine. The question is rated on a 5-point scale with responses ranging from "very unlikely" to "very likely."

The frequency and proportion of the responses will be summarized by study treatment and using Wilcoxon rank sum test for treatment comparison.

4.5. Tertiary Endpoints Analysis

4.5.1. Tertiary Subgroup Analyses

Subgroup analyses for GLP-1 RA use at randomization will be conducted by the methods described in Section 4.7.2.1.

4.5.2. Tertiary Efficacy Endpoints

For continuous endpoints, similarly to what described in Section 4.4.2.1 for the supportive secondary efficacy endpoints, either ANCOVA model using data from EAS1 or MMRM model using data from EAS2 will be performed.

For the binary outcome endpoints of percentage of participants at Week 52 achieving HbA1c <7%, HbA1c <7% without nocturnal level 2 or 3 hypoglycemia, HbA1c ≤6.5% without level 2 or 3 hypoglycemia, and HbA1c <7% without level 2 or 3 hypoglycemia, EAS1 will be used for the analysis and the details are provided in the following table:

Analysis population	All participants in EAS1 with non-missing baseline measure
Analysis data	All non-missing observations at Week 52 (Visit 31) during treatment period regardless of the use of study intervention or rescue therapy

Endpoint	• Binary outcome of HbA1c <7% with 1 indicating achieving HbA1c target
	• The composite of:
	  ○ binary outcome of HbA1c <7% at Week 52 with 1 indicating achieving HbA1c target; and
	  ○ binary outcome of no nocturnal hypoglycemia (<54 mg/dL or severe) during 52-week treatment period with 1 indicating no occurrence of nocturnal hypoglycemia.
	• The composite of:
	  ○ binary outcome of HbA1c ≤6.5% at Week 52 with 1 indicating achieving HbA1c target; and
	  ○ binary outcome of no hypoglycemia (<54 mg/dL or severe) during 52-week treatment period with 1 indicating no occurrence of hypoglycemia.
	• The composite of:
	  ○ binary outcome of HbA1c <7% at Week 52 with 1 indicating achieving HbA1c target; and
	  ○ binary outcome of no hypoglycemia (<54 mg/dL or severe) during 52-week treatment period with 1 indicating no occurrence of hypoglycemia.

Missing data handling	• For HbA1c, missing values at Week 52 (Visit 31) will be imputed using the same method for the primary endpoint. The binary outcomes of HbA1c <7% or ≤6.5% will be based on the imputed data. • For nocturnal hypoglycemia or hypoglycemia that are included in the composite endpoints, a participant who discontinued the treatment period before Week 52 (Visit 31) is considered as a non-responder (i.e. experienced the event) and the binary outcome value will be imputed as 0.

Analysis model	Each endpoint will be analyzed using a logistic regression model including treatment, strata (country, GLP-1 RA treatment at randomization and SU use at randomization), and baseline HbA1c value. The odds ratio between LY3209590 and insulin degludec will be used for treatment comparison. Multiple imputation will be performed, and the statistical inference will be based on the multiple imputation framework by Rubin (1987)

Abbreviations: EAS1 = Efficacy Analysis Set 1; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; SU = sulfonylurea.

4.5.3. Tertiary Safety Endpoints

For tertiary safety measures, the details are provided in Section 4.6 and the following subsections.

4.6. Safety Analyses

Safety measures include treatment exposure, adverse events (AE), vital signs, weight, hypoglycemia, laboratory measures and immunogenicity. All safety analyses will be based on the SS. Unless otherwise specified, safety analysis period will include both treatment period and follow-up period.

Percentages will be calculated using the safety population as the denominator. For events that are gender-specific, the denominator and computation of the percentage will include only participants from the given sex. Unless otherwise noted, Fisher's exact test will be used for treatment comparison, risk difference and 95% confidence intervals will be provided.

For continuous safety variables (for example, laboratory measures, vital signs, and weight), descriptive statistics for the observed values and change from baseline at scheduled visits during the treatment and follow-up period will be provided. For selected laboratory measures (i.e. liver enzyme tests, lipid measures), observed values, change from baseline and percentage change from baseline will be analyzed for the log-transformed values by the MMRM model using treatment, visit, and treatment by visit as fixed effect, baseline of the dependent variable as a covariate, and compound symmetry as the variance-covariance structure.

The incidence and event rate of participant-reported and CGM-based hypoglycemia will be summarized by treatment and analysis period for different types of hypoglycemia. Analysis details are provided in Section 4.6.3.1.

4.6.1. Extent of Exposure

Duration of exposure to study treatment will be summarized. No p-values will be reported in these tables as they are intended to describe the study populations, rather than test hypotheses about them. Total patient-years of exposure will be reported. The number and proportion of participants falling into the following different exposure categories will also be summarized by study treatment:

- >0, ≥30 days, ≥90 days, ≥180 days, ≥365 days; and
- >0 and <30 days, ≥30 and <90 days, ≥90 and <180 days, ≥180 and <365 days, ≥365 days.

Exposure on study treatment will be calculated as:

- LY3209590: date of the last treatment administration – date of first treatment administration + 7 days; and

- Insulin degludec: date of the last treatment administration – date of first treatment administration + 1 day.

Total patient-years of exposure will be calculated by the sum of duration of exposure in days divided by 365.25. The following summary statistics will be provided: n, mean, standard deviation, median, minimum, maximum, interquartile range, and total exposure (that is, total patient-years).

All participants who complete the study treatment period are required to complete a safety follow-up period and participants who discontinue the study treatment prematurely are encouraged to remain in the study for safety monitoring. The duration on study from the first dose of study treatment to the final study disposition date will also be summarized by treatment.

A listing of exposure to study treatment will be provided.

4.6.2. Adverse Events

Events that are newly reported after the first dose of investigational product (IP) or 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 (see the table in Section 4.1) will be used as baseline severity.

The table below describes the analysis related to AEs.

Analysis	Details
Overview of AEs	Number and percentage of participants who experienced: • SAE, • Death, • Discontinuation from study treatment due to an AE, • Discontinuation from study due to an AE, • TEAE, and • TEAE related to study treatment.
Summary by PT within SOC	Number and percentage of participants with AEs using MedDRA PT nested within SOC: • TEAE, • Maximum Severity TEAEs, • SAE, and • AE leading to permanent discontinuation of study treatment. Events will be ordered by decreasing risk difference within SOC. SOCs will be listed by decreasing risk difference. For each participant and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. The maximum severity will be determined based on the non-missing severities.

Analysis	Details
Summary by PT (within SMQ when applicable)	Number and percentage of participants with TEAEs using MedDRA PT (irrespective of SOC): • TEAEs occurring in ≥1% before rounding in LY3209590 group, and • TEAE of safety topic of interest by PT (within SMQ when applicable). Events will be ordered by decreasing risk difference.
Listing	Separate listings for the following AEs or events will be provided: • SAE including death; • AEs leading to study treatment discontinuation; • Severe hypoglycemia; • Events sent to the external adjudicator for MACE adjudication • Participants who receive rescue therapy due to severe/persistent hyperglycemia; • Persistent-recurrent hypoglycemia reported by investigators; • Persistent-recurrent hypoglycemia identified by programing; and • Medication errors of interest.

Abbreviation: AE = adverse event; LLT = lowest level term; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SOC = System Organ Class; PT = preferred term; TEAE = treatment emergent adverse event

4.6.2.1. Safety Topics of Interest

4.6.2.1.1. Severe Hypoglycemia

Severe hypoglycemia is a severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. The determination of a hypoglycemic event as an episode of severe hypoglycemia is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance. If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE case report form (CRF).

A summary of severe hypoglycemia by decreasing risk difference will be provided. The incidence and event rate during the treatment period will be analyzed using the method described in Section 4.6.3.1. A listing of severe hypoglycemia events will also be provided.

4.6.2.1.2. Persistent-Recurrent Hypoglycemia

The potential risk of persistent-recurrent hypoglycemia (P-R hypoglycemia) will be assessed from the first dose date up to the end of the study. P-R hypoglycemia events will be identified using:

1. investigator assessment and clinical judgment to determine if repeated hypoglycemia may have contributed to a hypoglycemic event that degenerated with poor outcomes, and
2. a prespecified criteria to derive events from e-diary database by programming (see definition in Appendix 10 [Section 6.10]).

Identification of P-R hypoglycemia based on investigator reporting is precipitated by a hypoglycemic event a participant or their caregiver informed as having resulted in a poor outcome. This information will trigger an e-mail alert notifying the investigator to contact the study participant, obtain more information about the specific hypoglycemic event, and provide the participant clinical guidance, if appropriate. Hypoglycemic events that trigger alerts to investigators are those participants or caregivers report in the e-Diary have required treatment with glucagon or IV glucose, resulted in coma, motor vehicle accident or other trauma, hospitalization, or emergency medical care.

Upon receiving the e-mail notification, investigator will access the e-diary database and answer the following question: *"In your clinical judgement, is this hypoglycemia event associated with repeated hypoglycemia events?".* Investigator should select *"Yes"* or *"No"* as an answer.

During protocol training, investigators are trained to consult the e-diary database and review participant's BG values and hypoglycemia reports to determine the best answer. If investigator judges the hypoglycemic event that triggered an alert is related to repeated episodes of hypoglycemia, the participant will be identified as having presented a P-R hypoglycemic event reported by the investigator.

P-R hypoglycemia events and participants who present P-R hypoglycemia will be identified by 1 or both approaches explained above. Summary statistics and a listing of the events identified by both methods will be provided.

4.6.2.1.3. Systemic Hypersensitivity Reactions

Hypersensitivity reactions are exaggerated or inappropriate immunologic responses occurring in response to an antigen or allergen. These can be systemic or localized. At all visits, participants will be evaluated by the investigator for signs and symptoms suggestive of hypersensitivity. Investigators will complete an CRF designed to record additional information about AEs suggestive of a hypersensitivity reaction. The TEAEs of hypersensitivity reactions were identified using:

- Anaphylactic reaction SMQ (20000021; narrow terms),
- Hypersensitivity SMQ (20000214; narrow terms), and
- Angioedema SMQ (20000024; narrow terms).

The number and percentage of participants who reported a TEAE for the following will be analyzed:

- Any narrow term from any 1 of the 3 SMQs indicated above (that is, combined search across narrow portions of all 3 SMQs), and
- Any narrow term within each SMQ, separately (that is, narrow SMQ search).

Individual PTs that satisfied the query will appear in the summary in decreasing order of risk difference between the LY3209590 and insulin degludec group.

The analyses above are the starting point for medical interpretation of any apparent differences between treatment groups. For notable events, case review will be applied to make the final determination of whether an event is most accurately described as a potential hypersensitivity reaction to study treatment, or another event that is not clearly associated with study treatment administration. This judgment will be on the basis of totality of information available, including the content of a follow-up CRF collected for potential hypersensitivity events.

4.6.2.1.4. Injection Site Reactions

Injection site reactions (ISR) are AEs localized to the immediate site of the administration of a medication. The evaluation of ISRs will be through the unsolicited reporting of ISR TEAEs and through the use of an Injection Site Reaction Follow-up Form completed by the investigator for each incidence of ISR. A summary of the number of participants with reported events meeting any of the following categories will be provided:

- MedDRA HLT of Injection site reactions;
- MedDRA HLT of Administration site reactions NEC;
- Lipodystrophies and localized amyloidosis, as represented by PTs of:
    - Lipoatrophy,
    - Lipodystrophy acquired,
    - Partial lipodystrophy,
    - Lipohypertrophy,
    - Sclerema, and
    - Cutaneous amyloidosis.

The summary will present:

- The number of participants reported at least one AE meeting any of the above categories,
- The number of participants reported any AE in each category, and
- The number of participants reported any AE for each PT within a specific category.

The PTs will be listed for summary within each category in decreasing risk difference.

The additional data collected on the ISR follow-up forms will be summarized in 2 distinct ways:

1. at the participant-level (each participant contributes to totals at most once, regardless of the number of ISR events the participant experienced), and

2. at the event level (each separate event contributes to totals, regardless of whether the participant experienced multiple ISR events).

4.6.2.1.5. Neoplasms

The TEAEs of neoplasms will be identified by narrow search for the following SMQ:

- Malignant tumours SMQ (20000194, narrow terms), and
- Tumours of unspecified malignancy SMQ (20000195, narrow terms).

A summary will present:

- Any narrow term from any 1 of the 2 SMQs indicated above (that is, combined search across narrow portions of both SMQs), and
- Any narrow term within each SMQ, separately (that is, narrow SMQ search).

4.6.2.1.6. Diabetic Ketoacidosis (DKA)

DKA will be searched by MedDRA PTs from all TEAEs. The number and percentage of participants experiencing treatment-emergent DKA will be summarized. The TEAEs of DKA will be identified using MedDRA PTs of:

- Diabetic ketoacidosis,

- Ketoacidosis,
- Euglycaemic diabetic ketoacidosis,
- Ketonuria,
- Diabetic ketosis,
- Diabetic ketoacidotic hyperglycaemic coma,
- Ketosis,
- Urine ketone body present,
- Blood ketone body,
- Blood ketone body increased,
- Urine ketone body,
- Blood ketone body present, and
- Lactic acidosis.

4.6.2.1.7. Diabetic Retinopathy or Maculopathy

The diabetic retinopathy or maculopathy will be searched by MedDRA PTs from all TEAEs. The list of PTs for the search is provided in Appendix 7 (Section 6.7). A summary of treatment-emergent retinopathy or maculopathy by PT will be provided.

4.6.2.1.8. Peripheral Edema

The peripheral edema will be searched by MedDRA PTs (see Section 6.8) from all TEAEs. The number and percentage of participants experiencing treatment-emergent peripheral edema will be summarized by PT.

4.6.2.1.9. Hypokalemia

The TEAEs of hypokalemia will be identified by narrow terms in Hypokalaemia SMQ (20000233). A summary of the number of participants with TEAEs meeting the SMQ narrow search criteria will be provided by PT.

4.6.2.1.10. Hyperglycemia

The study treatments were designed as the treatment of hyperglycemia for diabetes patients. Therefore, the hyperglycemia is usually not reported as an AE in diabetes studies. However, if a participant develops severe, persistent hyperglycemia after randomization, a rescue therapy will be considered. A listing of participants who receive rescue medication will be provided.

4.6.2.1.11. Major Adverse Cardiovascular Events (MACE)

Potential cerebrocardiovascular events will be identified by the investigative site or by a medical review conducted by the sponsor or designee. A blinded external Clinical Event Committee will adjudicate the events in a consistent and unbiased manner. Events include:

- Death;
- Cardiac ischemic events including:
    - myocardial infarction, and
    - hospitalization for unstable angina;
- cerebrovascular events including:
    - stroke, and

    - transient ischemic attack;
- hospitalization for heart failure; and
- coronary revascularization procedure.

Only confirmed MACE by the adjudication committee will be considered as AESIs. A listing of MACE events reported by investigator, including reported term and adjudication results, will be provided.

4.6.2.1.12. Medication Error of Interest

Medication Errors of Interest (MEI) are defined as medication error AEs (SMQ 20000224 - narrow and broad terms) that meet the criteria of important protocol deviations (IPD) indicative of multiple dose, according to the Trial Issue Management Plan (TIMP). These events are considered IPDs and special interest because of their potential to impact participant's safety.

MEI AEs are categorized as IPDs of "Investigational Medicinal Product and/or Investigational Device". Screening and identification of MEI AEs will occur during routine review of individual trial protocol deviations and trial level safety reviews.

The number and percentage of participants reported with MEI will be analyzed.

A listing of MEI will be provided. This listing will indicate if severe hypoglycemia or P-R hypoglycemia occurred after the MEI.

4.6.3. Additional Safety Assessments

4.6.3.1. Hypoglycemic Events

4.6.3.1.1. Participant-Reported Hypoglycemic Events

The following types of hypoglycemia events will be derived in the analysis data sets: documented hypoglycemia as Level 1, Level 2, and Level 3 (severe hypoglycemia) according to definitions based on the American Diabetes Association criteria where:

- Level 1: glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L);
- Level 2: glucose <54 mg/dL (3.0mmol/L); and
- Level 3: severe hypoglycemia (confirmed by the investigator to be an event that required assistance for treatment).

Level 2 and Level 3 events are considered clinically significant hypoglycemia. Therefore, the analysis on a composite of Level 2 and Level 3 (denoted as Level 2/3) hypoglycemia will also be conducted.

Hypoglycemia will also be further classified into:

- nocturnal hypoglycemia (occurs between midnight and 0600); and
- non-nocturnal hypoglycemia (occurs between 0600 and midnight).

If a hypoglycemic event is within 60 minutes of another hypoglycemic event, it is considered as a continuation of the previous event. If there are multiple hypoglycemic events within 60 minutes of each other, then all events will be combined into a single event, which has the:

- earliest date time;
- minimum glucose value, if applicable;
- maximum severity (Level 1, 2 or 3);
- combined all symptoms and outcomes; and
- time of nocturnal if any of the events is nocturnal;

of the multiple hypoglycemic events.

The combined event starts from the first record with Level 1, 2 or 3, and ends when there are no more events for at least 60 minutes.

The evaluation of potential persistent-recurrent hypoglycemia events will be through assessment of the clinically significant events confirmed by investigators based on clinical judgment and through events identified by a pre-specified criteria (Section 4.6.2.1.2 and Appendix 10, Section 6.10) using information based on the participant-reported hypoglycemia.

The details of planed analyses are provided in the below table.

Endpoint	Analysis Period	Statistical Method
Event rate of Level 1 hypoglycemia events (events/participant/year): • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 12-26, 26-52 weeks, post-treatment period	Negative binomial regression with treatment and baseline HbA1c as covariates, log (exposure/365.25 days) as the offset in the model.
Event rate of Level 2 hypoglycemia events (events/participant/year): • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 12-26, 26-52 weeks, post-treatment period	Negative binomial regression with treatment and baseline HbA1c as covariates, log (exposure/365.25 days) as the offset in the model. If the number of events is too small to run the negative binomial regression, exposure adjusted rate calculated by total number of events divided by total exposure for individual patients will be provided and the empirical method (see Appendix 9 [Section 6.9] for details) will be used for treatment comparison.
Event rate of Level 3 hypoglycemia events (events/participant/year): • All documented	baseline, 0-26, 0-52, 26-52 weeks, post-treatment period	Negative binomial regression with treatment and baseline HbA1c as covariates, log (exposure/365.25 days) as the offset in the model. If the number of events is too small to run the negative binomial

Endpoint	Analysis Period	Statistical Method
		regression, exposure adjusted rate calculated by total number of events divided by total exposure for individual participants will be provided and the empirical method (see Appendix 9 [Section 6.9] for details) will be used for treatment comparison.
Event rate of Level 2/3 hypoglycemia events (events/participant/year): • All documented • Nocturnal • Non-nocturnal	baseline, 0-6, 0-12, 0-26, 0-52, 12-26, 26-52 weeks, post-treatment period	Negative binomial regression with treatment and baseline HbA1c as covariates, log (exposure/365.25 days) as the offset in the model. If the number of events is too small to run the negative binomial regression, exposure adjusted rate calculated by total number of events divided by total exposure for individual patients) will be provided and the empirical method (see Appendix 9 [Section 6.9] for details) will be used for treatment comparison. The plots of the mean cumulative functions (MCFs) by each treatment arm will also be created. The population mean for cumulative number of events up to time t, M(t), will be estimated using a nonparametric estimation method described by Nelson (2003).
Incidence of Level 1 hypoglycemia events: • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 12-26, 26-52 weeks, post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates.
Incidence of Level 2 hypoglycemia events: • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 12-26, 26-52 weeks, post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates.
Incidence of Level 3 hypoglycemia events: • All documented	Baseline, 0-26, 0-52, 26-52 weeks, post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates.
Incidence of Level 2/3 hypoglycemia events: • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 12-26, 26-52 weeks, post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates.

Endpoint	Analysis Period	Statistical Method
• Nocturnal • Non-nocturnal		
Potential persistent-recurrent hypoglycemia events • identified by investigator • identified by pre-specified criteria (defined in Appendix 10 [Section 6.10])	Safety analysis period (see definition in Section 4.6)	The number of participants with at least one event will be summarized and compared by Fisher's exact test. The number of events will also be provided. Listings of the events will also be provided.

Abbreviations: HbA1c = hemoglobin A1c; Level 2/3 = Level 2 and Level 3 composite.

Note: The hypoglycemia yearly rate during defined period is calculated by the number of hypoglycemia within the period/number of days patient at risk within the period * 365.25. For rare events, 100-year rate will be provided. The hypoglycemia incidence during defined period indicates if the patient has at least 1 hypoglycemia events within the period (Yes/No).

Note: For treatment group comparison at baseline, baseline HbA1c is not included in the model.

A sensitivity analysis will be done for selected hypoglycemic endpoints where all hypoglycemic events are considered one hypoglycemic event until a succeeding glucose value is ≥ 70 mg/dL.

4.6.3.1.2. Hypoglycemic Events Derived from CGM

Level 2, Level 2 ending with BG value ≥70 mg/dL, and Level 1 or Level 2 hypoglycemic events collected from the sponsor provided CGM are defined in Appendix 6, Section 6.6.2. The analysis for incidence, event rate and duration are described in the table below. All data are included in the analysis. Missing data will be handled as described in Appendix 6.

Endpoint	CGM Session	Statistical Method
Event rate of Level 1 or Level 2 hypoglycemic events (events/participant/year): • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks (combine all sessions during treatment period), post-treatment period	Negative binomial regression with treatment and baseline HbA1c as covariates, log (exposure/365.25 days) as the offset in the model.

Endpoint	CGM Session	Statistical Method
Event rate of Level 2 hypoglycemic events (events/participant/year): • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks (combine all sessions during treatment period), post-treatment period	Negative binomial regression with treatment and baseline HbA1c as covariates, log (exposure/365.25 days) as the offset in the model. If the number of events is too small to run the negative binomial regression, exposure adjusted rate calculated by total number of events divided by total exposure for individual participants will be provided and the empirical method (see Appendix 9 [Section 6.9] for details) will be used for treatment comparison.
Event rate of Level 2 hypoglycemic events ending with ≥70 mg/dL (events/participant/year): • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks (combine all sessions during treatment period), post-treatment period	Negative binomial regression with treatment and baseline HbA1c as covariates, log (exposure/365.25 days) as the offset in the model. If the number of events is too small to run the negative binomial regression, exposure adjusted rate calculated by total number of events divided by total exposure for individual participants will be provided and the empirical method (see Appendix 9 [Section 6.9] for details) will be used for treatment comparison.
Incidence of Level 1 or Level 2 hypoglycemic events: • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks (combine all sessions during treatment period), post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates. The total number of episodes, number of episodes that includes Level 2 hypoglycemia episodes, and number of episodes that include glucose readings <54 mg/dL (3.0 mmol/L) but no Level 2 hypoglycemia episodes will be summarized for each CGM session.
Incidence of Level 2 hypoglycemic events: • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks (combine all sessions during treatment period), post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates.

Endpoint	CGM Session	Statistical Method
Incidence of Level 2 hypoglycemic events ending with ≥70 mg/dL: • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks (combine all sessions during treatment period), post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates.
Duration of Level 1 or Level 2 hypoglycemic events: • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks (combine all sessions during treatment period), post-treatment period	The MMRM model will include treatment, strata (country, baseline HbA1c stratum (<8.0%, ≥8.0%), GLP-1 RA treatment at randomization, and SU use at randomization), time and treatment-by-time interaction as fixed effects, and baseline duration as a covariate. **For 0-52 weeks:** ANCOVA model will include treatment, strata and baseline duration. **For Baseline and post-treatment period:** ANOVA models only include treatment.
Duration of Level 2 hypoglycemic events: • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks, post-treatment period	Same models as for Level 1 or Level 2 hypoglycemic events. A listing will be provided for participants with Level 2 hypoglycemia episodes lasting >360 minutes
Duration of Level 2 hypoglycemic events ending with BG ≥70 mg/dL: • 24-hour	Baseline, 0-4, 8-12, 22-26, 48-52, 0-52 weeks, post-treatment period	Same models as for Level 1 or Level 2 hypoglycemic events.

Abbreviations: HbA1c = hemoglobin A1c.

Note: The hypoglycemic yearly rate during defined period is calculated by number of hypoglycemic events within the period/number of days patient at risk within the period * 365.25. The hypoglycemia incidence during defined period indicates if the patient has at least 1 hypoglycemic event within the period (Yes/No).

4.6.3.2. Laboratory and Adverse Event for Hepatic Safety

Hepatic labs include:

- alanine aminotransferase (ALT),
- aspartate aminotransferase (AST),
- total bilirubin (TBL),
- direct bilirubin (DBL),
- serum alkaline phosphatase (ALP), and

- gamma-glutamyltransferase (GGT).

When criteria are met for hepatic evaluations, investigators will conduct close monitoring of hepatic symptoms and liver tests, perform a comprehensive evaluation for alternative causes of abnormal liver tests, and complete follow-up hepatic safety CRFs.

The table below lists summary TFLs for the analysis of hepatic laboratory data.

Analysis	**Details**
Abnormal postbaseline categories – hepatic safety parameters	ALT: The number and percentage of participants with a measurement greater than or equal to 1 time (1×), 3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. AST: The number and percentage of participants with a measurement greater than or equal to 1 time (1×), 3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. ALP: The number and percentage of participants with a measurement greater than or equal to 2 times (2×) and 3 times (3×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. TBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2×), 5 times (5×), and 8 times (8×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. DBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2×) and 5 times (5×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. GGT: The number and percentage of participants with a measurement greater than or equal to 2 times (2×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value.
Treatment-emergent potentially drug-related hepatic disorders	Potentially drug-related hepatic disorders are defined using a custom query based on the following SMQs: • Broad and narrow terms in the Liver-related investigations, signs and symptoms SMQ (20000008); • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009); • Broad and narrow terms in the Hepatitis non-infections SMQ (20000010); • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013); and • Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015).

Analysis	Details
	These SMQs are a subset of the sub-SMQs comprising the full Hepatic Disorders SMQ. Only the sub-SMQs considered applicable to capturing potentially drug-related hepatic disorders are included. The percentage of study participants with at least one of any of the MedDRA preferred terms from any of the above SMQs will be summarized in addition to the percentages for each MedDRA preferred term.
Hepatocellular drug-induced liver injury screening plot (TBL vs ALT or AST)	Each participant's data is plotted based on their maximum postbaseline TBL (y-axis) and transaminase (ALT or AST, whichever is higher), regardless of the time between the 2 maximum values. Lines represent TBL and transaminase cutoffs of 2× ULN and 3× ULN, respectively. A potential Hy's law case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2× ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3× ULN, without cholestasis (defined as ALP less than 2× ULN).
Hepatocellular drug-induced liver injury screening table	The percentages of study participants falling in each of the 3 relevant quadrants of the plot (right upper, left upper, right lower) will be summarized in a table.
Cholestatic drug-induced liver injury screening plot (TBL vs ALP)	Each participant's data is plotted based on their maximum postbaseline TBL (y-axis) and ALP (x-axis), regardless of the time between the 2 maximum values. Lines represent TBL and ALP cutoffs of 2× ULN and 3× ULN, respectively. A potential cholestatic liver injury case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2× ULN within 30 days after maximum postbaseline ALP equal to or exceeding 3× ULN.
Cholestatic drug-induced liver injury screening table	The percentages of study participants falling in each of the 3 relevant quadrants of the plot (right upper, left upper, right lower) will be summarized in a table.
List of Participants with potential hepatocellular drug-induced liver injury	Includes participants falling in the right upper quadrant in the Hepatocellular Drug-Induced Liver Injury Screening plot.
List of Participants with potential cholestatic drug-induced liver injury	Includes participants falling in the right upper quadrant in the Cholestatic Drug-Induced Liver Injury Screening plot.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; DBL = direct bilirubin; GGT = gamma-glutamyl transferase; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TBL = total bilirubin; ULN = upper limit of normal.

Planned and unplanned measurements will be included. The measurements do not need to be taken at the same blood draw.

4.6.3.3. Clinical Laboratory Evaluations

For the following selected laboratory measures:

- Liver enzyme tests: ALT, ALP, AST, GGT, DBL and Total Bilirubin, and
- Lipid measures: Triglycerides, total cholesterol, LDL-C, and HDL-C (results from fasting samples).

MMRM model (as described in Section 4.6) will be used for the observed values, change from baseline and percentage change from baseline, for which log-transformation will be applied. Geometric LS means will be provided. Analyses will be provided in both international units (SI) and conventional units (CN) if they are different.

Box plots with descriptive statistics for the observed values and change from baseline will be provided by treatment group and visit.

For other laboratory measures, descriptive summaries will be provided for the observed values and change from baseline by treatment group and visit.

The percentages of patients with elevated or low values meeting specified levels (see Appendix 11, Section 6.11) at any time postbaseline (including scheduled and unscheduled measurements) will be summarized and compared between treatment groups using risk difference and 95% confidence interval.

A listing of abnormal laboratory analytes collected quantitatively (high or low during postbaseline using Level 2 definitions in Appendix 11, Section 6.11) and qualitatively (abnormal during postbaseline) will be provided, including participant identification, treatment group, laboratory sample collection day (that is, days from start of study drug), analyte name, abnormal result, and reference low or high limits (Level 2 cut-off value).

Scatter plots of maximum-by-maximum measurements and minimum-by-minimum measurements will not be created a-priori. They may be created if warranted after review of the planned tables and figures, using Figures 6.3 and 6.4 from the Analysis and Displays for Labs white paper (PHUSE 2022) as the model. ADaM datasets will include variables to enable the creation of scatter plots for use in either an interactive tool or for ad-hoc figures.

4.6.3.4. Vital Signs and Physical Characteristics

The planned summaries are provided in the Table below. The measurements analyzed for vital signs and physical characteristics include systolic BP, diastolic BP, pulse, weight, and BMI.

Analysis Type	Analysis Details
Observed values change by visit	• Includes all participants in the safety population who have both a baseline and at least 1 postbaseline observation • MMRM model (as described in Section 4.6) will be used. See also: Table 6.2 from the Analyses and Displays for Labs white paper (PHUSE 2022)
Summary by category	• Definitions provided in Tables 31-33 from FDA's September 2022 Standard Safety Tables and Figures document will be used for the numerator. ○ Systolic BP (mm Hg): ▪ Low: Level 1: <90 ▪ High: Level 1: ≥90, Level 2: ≥120,

Analysis Type	Analysis Details
	Level 3: ≥140, Level 4: ≥160, Level 5: ≥180 ○ Diastolic BP (mm Hg): ▪ Low: Level 1: <60 ▪ High: Level 1: ≥60, Level 2: ≥90, Level 3: ≥110, Level 4: ≥120 • Includes participants with at least one postbaseline measurement… • Statistical comparisons (using methods described in Section 4.6) will be included.
Participants meeting CTCAE grade changes in weight	For weight, cutoffs informed by CTCAE version 5 (Grades 1-3) will be used: ○ (Loss) decrease: Level 1: ≥5%, Level 2: ≥10%, Level 3: ≥20% ○ (Gain) increase: Level 1: ≥5%, Level 2: ≥10%, Level 3: ≥20% Includes participants with both a baseline and at least 1 postbaseline observation. Statistical comparisons (using methods described in Section 4.6) will be included.

Abbreviations: BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; FDA = Food and Drug Administration; MMRM = mixed-model repeated measures.

Scatter plots to support vital sign evaluations

Scatter plots of maximum-by-maximum measurements and minimum-by-minimum measurements will not be created a-priori. They may be created if warranted after review of the planned tables and figures, using Figures 6.3 and 6.4 from the Analysis and Displays for Labs white paper (PHUSE 2022) as the model. ADaM datasets will include variables to enable the creation of scatter plots for use in either an interactive tool or for ad-hoc figures.

4.6.4. Device Product Complaints

A summary of all product complaints, inclusive of device product complaints that lead to an AE and/or SAE will be included by category. Additional summaries may be provided as deemed appropriate.

4.7. Other Analyses

4.7.1. Immunogenicity

A participant is evaluable for TE ADA if the participant has a nonmissing baseline ADA result, and at least 1 nonmissing postbaseline ADA result.

A participant who is evaluable for TE ADA is TE ADA+ if either of the following holds:

- Treatment-induced ADA: the participant has baseline status of ADA Not Present and at least 1 postbaseline status of ADA Present with titer ≥1:40, which is 2 × minimum required dilution (MRD) of the ADA assay (MRD=1:20).
- Treatment-boosted ADA: the participant has baseline status of ADA Present and at least 1 postbaseline status of ADA Present with the titer being ≥2 dilutions (4-fold) of the baseline titer. That is, the participant has baseline (B) status of ADA Present, with titer 1:B, and at least 1 postbaseline (P) status of ADA Present, with titer 1:P and P/B≥4.

Refer to PSAP for all definitions and additional details for immunogenicity.

All analyses will be based on all evaluable TE ADA participants. The baseline ADA status will be summarized by treatment group. The number and percentage of participants who are TE ADA+ will be summarized by treatment group. The summary will include the number and percentage of participants with treatment-induced ADA and treatment boosted ADA. A summary of titer values will be provided for participants who are TE ADA positive. This analysis will be performed for the following periods:

- The treatment period up to treatment discontinuation, and
- The entire postbaseline period, including safety follow-up.

A number of additional analyses of the immunogenicity data from this study will be presented in an integrated summary document, alongside data from other studies. The analyses to be performed are described in the PSAP.

4.7.2. Subgroup analyses

The interaction effects will be evaluated using a significance level of 0.05, unadjusted. Subgroup analyses will be conducted as defined in this section. Additional subgroup analysis may also be performed as appropriate.

4.7.2.1. Subgroup analyses for GLP-1 RA use at randomization

The following outcomes will be included in the subgroup analyses for GLP-1 RA use at randomization:

- rate of participant-reported Level 1 hypoglycemia events during Weeks 0 to 26, Weeks 26 to 52, and Weeks 0 to 52;
- rate of participant-reported composite of Level 2 and 3 hypoglycemia events during Weeks 0 to 26, Weeks 26 to 52, and Weeks 0 to 52;
- change from baseline to Week 26 and Week 52 in body weight;
- insulin dose at Week 26 and Week 52; and
- measurements collected during CGM sessions collected prior to Weeks 12, 26, and 52 of:
    - time in hypoglycemia with glucose <70 mg/dL (3.9 mmol/L),
    - time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L),
    - time in hyperglycemia defined as glucose >180 mg/dL (10.0 mmol/L), and
    - time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive.

The hypoglycemia rates will be analyzed using a negative binomial regression including the same independent variables for hypoglycemia event analyses (see Section 4.6.3.1) plus 2-way interaction of GLP-1 RA use at randomization and treatment.

Analyses for change from baseline in body weight will be performed by the MMRM model using the same independent variables as described in Section 4.6.3.4 plus GLP-1 RA use at randomization, 2-way interaction of GLP-1 RA use at randomization and visit, and 3-way interaction of treatment, visit and GLP-1 RA use at randomization.

Analyses for insulin dose and CGM parameters will be performed by the MMRM model using the same independent variables as described in Section 4.4.2.1 plus 2-way interaction of GLP-1 RA use at randomization and visit, and 3-way interaction of treatment, visit and GLP-1 RA use at randomization.

Separate analysis without the terms related with the subgroup will be performed for each subpopulation.

4.7.2.2. Subgroup analyses for HbA1c

Subgroup analyses in HbA1c and change in HbA1c from baseline to Week 52 will be conducted with subgroups defined as (a subgroup category will not be included if there are less than 10 participants in the category):

- Age (<65 years and ≥65 years),
- Baseline HbA1c stratum (<8.0% and ≥8.0%),
- Ethnicity,
- Gender,
- Race (white, Asian, American Indian or Alaska Native, Black or African American),
- Region (US and non-US),
- Region (North America, South America, Europe, Asia),
- SU use at randomization,
- Estimated Glomerular Filtration Rate (eGFR) at baseline (<60, 60 - <90, and ≥90 mL/min/1.73 m^2), and
- Duration of diabetes (<median and ≥median).

Analyses for HbA1c and its change will be performed within each subgroup using the same MMRM model for efficacy estimand described for the primary analysis in Section 4.3.2. In addition, the interaction effects will be assessed using the model including the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit and the subgroup.

Another subgroup analysis for HbA1c will be conducted for treatment regimen estimand. The ANCOVA analysis for HbA1c for the treatment regimen estimand as described in Section 4.3.2 will be performed within each subgroup. The statistical inference will be based on the multiple imputation framework by Rubin (1987). The p-value for treatment by subgroup interaction will be calculated using a chi-square test based on estimated treatment differences within each subgroup (see details in Appendix 12 [Section 6.12]).

4.7.2.3. Subgroup analyses in hypoglycemia

Subgroup analyses of documented Level 2/3 hypoglycemia, non-nocturnal and nocturnal hypoglycemia rates during 0-52 weeks will be conducted. The subgroups are defined as:

- Baseline HbA1c stratum (<8.0% and ≥8.0%),
- Region (US and non-US),
- Region (North America, South America, Europe, Asia), and

- SU use at randomization.

Estimated glomerular filtration rate (eGFR) at baseline (<60, 60 - <90, and ≥90 mL/min/1.73 m^2) The hypoglycemia rates will be analyzed using a negative binomial regression including the same independent variables for hypoglycemia event analyses (see Section 4.6.3.1) plus factors of subgroup, 2-way interaction of subgroup and treatment.

Separate analysis without the terms related with the subgroup will be performed for each subpopulation.

4.8. Interim Analyses

4.8.1. Data Monitoring Committee (DMC)

An independent external DMC will be responsible for reviewing unblinded data during the study. The committee will include 4 clinicians and 1 statistician who are independent experts not involved in the study. The DMC will review unblinded safety data to ensure the safety of study participants and some efficacy data to confirm a reasonable risk-benefit profile. A subset of analyses described above in Sections 4.3 to 4.6 will be provided for the DMC review. The external Statistical Analysis Center statistician/analyst will generate the unblinded reports and confidentially distribute the unblinded reports to DMC members. Study team will remain blinded to study treatment until the planned unblinding occurs. The DMC will be conducted to maintain study integrity. Details of DMC is included in the DMC charter.

4.9. Changes to Protocol-Planned Analyses

There are no changes but additional details are provided to the analyses described in the protocol.

5. Sample Size Determination

Approximately 888 participants will be randomly assigned to LY3209590 and insulin degludec in a 1:1 ratio. With the assumption of 15% dropout at Week 52, approximately 377 and 377 participants will complete 52 weeks of treatment on LY3209590 and insulin degludec, respectively.

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control as measured by change from baseline to Week 52 (Visit 31) in HbA1c in participants with T2D who are starting basal insulin for the first time. A total of 754 completers (377 on LY3209590 and 377 on insulin degludec) will provide an at least 99% statistical power to show noninferiority between LY3209590 and insulin degludec using the upper limit of a 2-sided 95% confidence interval (LY3209590 – insulin degludec) and these assumptions:

- a NIM of 0.4%,
- no true difference between treatment groups, and
- an SD of 1.1%.

This sample size also has at least 95% statistical power to show noninferiority between LY3209590 and insulin degludec using a 0.3% NIM at Week 52.

The number of participants in each subpopulation of background treatment will be approximately 50% of the study population with balanced treatment assignment to support the following secondary objectives, controlled for Type 1 error:

- To demonstrate noninferiority of LY3209590 to insulin degludec in HbA1c change from baseline to Week 52 for the subpopulation of participants using GLP-1 RAs; and
- To demonstrate noninferiority of LY3209590 to insulin degludec in HbA1c change from baseline to Week 52 for the subpopulation of participants not using GLP-1 RAs.

In each subpopulation, 188 completers for each study intervention will provide an approximately 90% statistical power to show noninferiority between LY3209590 and insulin degludec using the upper limit of a 2-sided 95% confidence interval (LY3209590 – insulin degludec) and these assumptions:

- a NIM of 0.4%,
- no true difference between treatment groups, and
- an SD of 1.1%.

The 754 completers will provide 95% statistical power to demonstrate the superiority of LY3209590 versus insulin degludec, of change in HbA1c from baseline to 52 weeks, assuming an SD of 1.1% and true mean difference is -0.3%, using the alpha of 0.05.

The 754 completers will provide at least 95% statistical power to show the superiority of the percentage of time in glucose range between 70 and 180 mg/dL inclusive during the CGM session prior to Week 52 between LY3209590 and insulin degludec, assuming an SD of 18% and true mean difference is 5%, using the alpha of 0.05.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Demographic and baseline characteristics including but not limited to age (years), age groups (<65, ≥65 and <75, ≥75 and <85, ≥85 years), sex, ethnicity, race, country, region, height, weight (kg), body mass index (BMI: kg/m2), BMI groups (<25, ≥25 and <30, ≥30 and <35, ≥35 kg/m^2), eGFR groups (<30, ≥30 and <60, ≥60 and <90, ≥90 mL/min/1.73 m^2), eGFR categories by SU use, duration of diabetes (years), HbA1c at screening, HbA1c stratum at screening (<8.0% and ≥8.0%), baseline HbA1c, baseline HbA1c stratum (<8.0% and ≥8.0%), fasting serum glucose (mmol/L and mg/dL), GLP-1 RA treatment at randomization, SU use at randomization and number of non-insulin antihyperglycemic medication use at randomization will be summarized by treatment group using the mITT and Randomized Population (if different from the mITT).

Continuous measures will be summarized using descriptive statistics and treatment difference will be analyzed using the analysis of variance. Categorical measures will be summarized using sample size, frequency, and percentage and treatment difference will be analyzed using Chi-squared test.

The by-participant listing of demographic and baseline characteristics will be provided for Randomized Population.

Historical conditions are conditions that end prior to inform consent and preexisting conditions are conditions that are still ongoing at inform consent. The number and percentage of participants with historical conditions will be summarized by treatment group using MedDRA PT using the mITT and Randomized Population (if different from the mITT). Events will be ordered by decreasing frequency within SOC. Similar summary will also be provided for preexisting conditions.

6.2. Appendix 2: Treatment Compliance

Treatment compliance will be summarized using the mITT population excluding inadvertently enrolled participants.

The study protocol provides dosing algorithms for both study treatments. The investigator will calculate the algorithm recommended dose based on participant's fasting blood glucoses and hypoglycemia occurrence reported in e-diary. If the investigator does not agree with the algorithm recommended dose, the investigator will prescribe another dose for the participant and choose a reason for not following the algorithm recommended dose from a picklist. The number and percentage of investigator prescribed doses different from algorithm recommended doses will be provided to evaluate investigator's adherence to the dosing algorithm. The reasons for not following the algorithm recommended dose will also be summarized.

The first dose of study treatment is administered by site personnel at the site and the subsequent doses are self-administered by the participants. The number and percentage of investigator prescribed doses that are not equal to participant administered dose will be provided.

6.3. Appendix 3: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and "Other" Non-Serious Adverse Events are summarized: by treatment group, by MedDRA PT.
- An AE is considered "Serious" whether or not it is a TEAE.
- An AE is considered in the "Other" category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event,
    - the number of participants who experienced each event term, and
    - the number of events experienced.
- For each Serious AE, these additional terms are provided for EudraCT:
    - the total number of occurrences causally related to treatment,
    - the total number of deaths, and
    - the total number of deaths causally related to treatment.
- Consistent with www.ClinicalTrials.gov requirements, "Other" AEs that occur in fewer than 5% of patients/subjects in every treatment group may be excluded if a 5% threshold is chosen. Allowable thresholds include 0% (all events), 1%, 2%, 3%, 4% and 5%.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.
- Demographic table including the following age ranges required by EudraCT: in utero, preterm newborn infants (gestational age <37 weeks), newborns (0-27 days), infants and toddlers (28 days – 23 months, children (2-11 years), adolescents (12-27 years), adults (18-64 years), 65-85 years, and 85 years and over.

6.4. Appendix 4: Concomitant Medication

Concomitant therapy is defined as the therapy that starts before, on, or after the first day of study treatment and before the last dose date in the treatment period, and continues into the treatment period, that is, either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment.

The number and percentages of participants who take concomitant medication will be summarized by treatment using PTs nested within Anatomical Therapeutic Chemical (ATC). The concomitant medications will be ordered by decreasing frequency of LY3209590 within each ATC.

6.5. Appendix 5: Protocol Deviations

IPDs are the deviations from the study protocol that may compromise data integrity and patients' safety. The IPD categories and details of IPD identification are provided in the trial issue management plan.

The number and percentage of participants with any reported IPDs will be summarized by treatment group and IPD category. The IPDs identified by site monitoring and clinical database will be integrated. If the IPD is identified by both methods, only the site monitoring IPD will be presented.

6.6. Appendix 6: Derivation of CGM Variables

Blinded CGM will be worn by participants at the following designated weeks:

- Two weeks in screening/lead-in period with the data download at Visit 3 (Week 0),
- Four weeks after the initiation of study treatment with the data download at Visit 7 (Week 4),
- Four weeks from V7 (Week 4) with the data download at Visit 11 (Week 8) (only for sites in Japan),
- Four weeks near the end of weekly titration period with the data download at Visit 15 (Week 12),
- Four weeks near the end of half year treatment with the data download at Visit 24 (Week 26),
- Four weeks near the primary endpoint with the data download at Visit 31 (Week 52), and
- Four weeks after the end of study treatment period with the data download at Visit 802 (Week 57).

Dexcom G6 system will be used in all countries to collect CGM data except China. In China, Libre Freestyle H system will be used instead.

Linear interpolation will be used to impute the missing glucose readings during intervals >7 minutes and ≤15 minutes. Missing data will be imputed at a 5-minute interval using the BG value before and the one after the interval.

For example, the BG reading before the interval is 50 mg/dL at time 100 min, and the BG reading after interval is 70 at time 115 min, then the missing records will be imputed as:

- at time 105 min, BG reading=50+5*(70-50)/(115-100)=56.7, and
- at time 110 min, BG reading=50+10*(70-50)/(115-100)=63.3.

Glucose reading intervals >15 minutes will be treated as missing data and not be counted in the length of the analysis periods. Since the Libre Freestyle H system normally provides readings every 15 minutes, the linear interpolation missing data imputation will not be performed.

As shown in the table below, all the CGM derivations are based on the data from valid CGM periods of a day and sessions unless otherwise specified.

Minimum Data Available to Define a Valid Period of the Day and CGM Session

Period	Definition of Valid Period	Definition of Valid CGM Session
Valid CGM Day (00:00-23:59)	≥70% of expected values available (≥202 of 288 values for Dexcom G6 system; ≥ 68 of 96 values for Libre Freestyle H system)	≥ 3 valid CGM days within a visit define a valid CGM visit. A valid CGM session only includes valid CGM visits.
Valid CGM Nighttime (00:00-05:59)	≥70% of expected values available (≥50 of 72 values for Dexcom G6 system; ≥ 17 of 24 values for Libre Freestyle H system)	≥ 3 valid CGM Nighttime period within a visit define a valid CGM visit. A valid CGM session for nighttime only includes valid CGM visits.
Valid CGM Daytime (06:00-23:59)	≥70% of expected values available 151 of 216 values for Dexcom G6 system; ≥ 50 of 72 values for Libre Freestyle H system)	≥ 3 valid CGM Daytime period within a visit define a valid CGM visit. A valid CGM session for Daytime only includes valid CGM visits.

For the primary analysis, CGM data meeting minimal completeness criteria for the period, visit and the session as defined in the table above will be used. Sensitivity analysis will be done for selected parameters including all CGM data.

The ambulatory glucose profile during the 24-hour period will be generated with interquartile ranges, at treatment-group level by CGM session, based upon the observed and imputed CGM measures.

6.6.1. Glucose in Target Ranges, Hypoglycemia or Hyperglycemia

The following variables of time in range, hypoglycemia, hyperglycemia during each CGM session will be derived:

- 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 nighttime period (defined as midnight to 0600 hours), the daytime period (defined as 0600 hours to 2400 hours) and a 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] and ≥54 mg/dL [3.0 mmol/L]) during the nighttime period, the daytime period and a 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 the nighttime period, the daytime period and a 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]) during the nighttime period, the daytime period and a 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within a hyperglycemic range (defined as >250 mg/dL [13.9 mmol/L]) during the nighttime period, the daytime period and a 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 [13.9 mmol/L]) during the nighttime period, the daytime period and a 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within a glucose range (defined as between 70 mg/dL and 180 mg/dL [3.9 and 10.0 mmol/L]) inclusive during the nighttime period, the daytime period and a 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within a glucose range (defined as between 70 mg/dL and 140 mg/dL [3.9 and 7.8 mmol/L] inclusive) during the nighttime period, the daytime period and a 24-hour period.

The percentage of time within a glucose range (target, hypoglycemia 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 (for example, 24-hour period). The average percentage of time among valid CGM days for the corresponding time interval during each CGM session will be used in the analysis.

The duration (in minutes) within the glucose range will then be calculated as the average percentage of time within the glucose range times the length of the period (24-hour, 18 hour, and 6 hour, for the periods of 24 hour, daytime or nighttime, respectively).

According to the guidance (Battelino et al. 2019), the following CGM targets of glycemic control will also be derived during a 24-hour period:

- The percentage of time within a normal glycemia range (defined as between 70 mg/dL and 180 mg/dL [3.9 and 10.0 mmol/L] inclusive) >70%;
- The percentage of time within a hypoglycemia range (defined as <70 mg/dL [3.9 mmol/L]) <4%;
- The percentage of time within a hypoglycemia range (defined as <54 mg/dL [3.0 mmol/L]) <1%;
- The percentage of time within a hyperglycemic range (defined as >180 mg/dL [10.0 mmol/L]) <25%; and
- The percentage of time within a hyperglycemic range (defined as >250 mg/dL [13.9 mmol/L]) <5%.

In addition, according to the guidance in 2023 (Battelino et al. 2023), 2 composite endpoints will be derived during a 24-hour period:

- >70% time in range 70 -180 mg/dL (3.9 - 10.0 mmol/L inclusive) and <4% time below range <70 mg/dL (<3.9 mmol/L); and
- >70% time in range 70 -180 mg/dL (3.9 - 10.0 mmol/L inclusive) and <1% time below range <54 mg/dL (<3.0 mmol/L).

The daily duration (in minutes) of time within a glucose range (defined as <54 mg/dL [3.0 mmol/L]; <70 mg/dL [3.9 mmol/L] and ≥54 mg/dL [3.0 mmol/L]; <70 mg/dL [3.9 mmol/L]; ≥70 mg/dL [3.9 mmol/L] and ≤140 mg/dL [7.8 mmol/L]; ≥70 mg/dL[3.9 mmol/L] and ≤180 mg/dL [10.0 mmol/L]; >180 mg/dL[10.0 mmol/L] and ≤250 mg/dL[13.9 mmol/L]; >250 mg/dL [13.9 mmol/L]) will be merged with the dose administration data to get the summary of daily time in each glucose range since dose administration in each CGM session in the treatment period. For LY3209590, days relative to dose administration will be derived as 0 (dosing day), and then 1, 2, …, up to 6 days after most recent dose administration but before the next dose administration. The average daily time in each glucose range for the given day (0 to 6) relative to the dose administration among valid CGM days (with at least 70% of the data each day) during each CGM session will be used in the analysis.

6.6.2. Hypoglycemic Episode

According to the International Consensus Statement (Battelino et al. 2023), the CGM-determined hypoglycemic episodes for Level 1 or 2 and Level 2 are defined as below:

- **Level 2 hypoglycemia (BGs<54 mg/dL):**
  - **Starting time:** is the time of the **1st** BG of BGs <54 mg/dL for ≥15 consecutive minutes (regardless of number of BG readings);
  - **Ending time:** is the time of the **last** BG of the BGs ≥54 mg/dL for ≥15 consecutive minutes (regardless of number of BG readings); and
  - **Duration:** Time of the **last** BG <54 mg/dL – the time of the **1st** BG <54 mg/dL;
- **Level 1 or 2 hypoglycemia (BGs<70 mg/dL):**
  - **Starting time:** is the time of the **1st** BG of BGs <70 mg/dL for ≥15 consecutive minutes (regardless of number of BG readings);
  - **Ending time:** is the time of the **last** BG of the BGs ≥70 mg/dL for ≥15 consecutive minutes (regardless of number of BG readings); and
  - **Duration:** Time of the **last** BG <70 mg/dL - the time of the **1st** BG <70 mg/dL; and
- **Level 2 hypoglycemia ending with BG ≥70 mg/dL (start with BG <54mg/dL, end with BG ≥70 mg/dL):**
  - **Starting time:** is the time of the **1st** BG of BGs <54 mg/dL for ≥15 consecutive minutes (regardless of number of BG readings);
  - **Ending time:** is the time of the BG that ensures the BGs ≥70 mg/dL for 15 consecutive minutes (regardless of number of BG readings); and
  - **Duration:** Time of the **last** BG <70 mg/dL – the time of the **1st** BG <54 mg/dL.

For the Dexcom G6 system, if the truncated time interval is >7 and ≤15 minutes, use linear interpolation to impute the missing data at 5-minute intervals as described in Section 6.6.

If the truncated time interval is >15 minutes:

- at any time, which make the starting time undeterminable, then do not count this time interval and no episodes start;
- If it is after an episode started, which makes the ending time undeterminable, then the episode ends at the starting time of the truncation; and
- If an episode started and continued until the end of a CGM session, then the episode ends at the end of CGM session.

The Libre Freestyle H system determined hypoglycemic episodes for level 1 or 2 and level 2 are defined similarly as for Dexcom G6 system.

The average duration, incidence, event rate of the Level 1 or 2 and Level 2 hypoglycemia episodes will be analyzed for each CGM session. The average duration will be calculated by dividing the sum of the duration of individual episodes during the given CGM session by the number of episodes, and used in the analysis.

The hypoglycemia event rate (events/participant/year) will be calculated by dividing the number episodes by the number of CGM days × 365.25 days.

The duration (minutes) for a day = the time of last CGM value - the time of the 1st CGM value - the sum of intervals that are >15 minutes within each CGM day.

6.6.3. Mean Glucose and Glucose Management Indicator

The average glucose within a time period (a 24-hour period, daytime or nighttime) for each valid CGM day will be calculated first and then the average of daily average for a CGM session will be used as the mean glucose of the CGM session in the analysis.

The glucose management indicator (GMI) is a new parameter estimating A1c from CGM. The GMI is based on the above mean glucose (24-hour period) by CGM using the below formula (Bergenstal et al. 2018):

$$\text{GMI}(\%) = 3.31 + 0.02392 \times \text{mean glucose (mg/dL)}$$

6.6.4. Glycemic Variability

Glycemic variability will be derived 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 valid CGM day within a visit;
- m represents the number of valid CGM days in the specific time period at a visit; and
- $BG_{k,i}$ represents the glucose value at time point i on day k unless otherwise specified.

Sections 6.6.4.1 and 6.6.4.2 provide the derivation method for variables assessing within-day and between-day glucose variability based on CGM readings.

6.6.4.1. Within-Day Variability

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

Within-day glucose SD (Rodbard 2009):

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

Within-day glucose CV (Clarke and Kovatchev 2009):

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

The low blood glucose index (LBGI), high blood glucose index (HBGI), and blood glucose risk index (BGRI) will be calculated using the following standard formulas (Kovatchev et al. 2006).

The LBGI, HBGI, and BGRI will be derived for each valid CGM day of a visit and then average across days within a CGM session. The calculations of LBGI, HBGI and BGRI take the following steps:

1. For each blood glucose (BG [mg/dL]) at the i^{th} time point, compute the following:

$$f(BG_i) = 1.509\times[(\ln(BG_i))^{1.084}-5.381]$$

2. Compute BG risk for each reading

$$rl(BGi)=10\times f(BG_i), \text{ if } f(BG_i) <0; \text{ otherwise } rl(BG_i) = 0$$
$$rh(BGi)=10\times f(BG_i), \text{ if } f(BG_i) >0; \text{ otherwise } rh(BG_i) = 0$$

3. Compute LBGI and HBGI

$$LBGI = \frac{1}{n}\sum_{i=1}^{n} rl(BG_i)$$

$$HBGI = \frac{1}{n}\sum_{i=1}^{n} rh(BG_i)$$

4. Compute BGRI

$$BGRI = LBGI + HBGI$$

6.6.4.2. Between-Day Variability

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

Between-day glucose SD (Rodbard 2009):

$$SD = \frac{1}{n}\sum_{i=1}^{n} SD_i = \frac{1}{n}\sum_{i=1}^{n} \sqrt{\frac{\sum_{k=1}^{m}(BG_{k,i} - \left\{\frac{\sum_{k=1}^{m} BG_{k,i}}{m}\right\})^2}{m-1}}$$

Between-day glucose CV (Kovatchev et al. 2009):

$$CV = \frac{1}{n}\sum_{i=1}^{n} CV_i = \frac{1}{n}\sum_{i=1}^{n} \frac{SD_i}{\left(\frac{\sum_{k=1}^{m} BG_{k,i}}{m}\right)} \times 100$$

Mean of daily differences (MODD): this parameter is calculated as the mean of absolute differences between glucose values at corresponding time points of consecutive days.

$$MODD = \frac{1}{m-1}\sum_{k=1}^{m-1} \frac{\sum_{i=1}^{n} \left| BG_{k+1,i} - BG_{k,i} \right|}{n}$$

6.7. Appendix 7: MedDRA PT for Diabetic Retinopathy or Maculopathy

The following PT will be used to identify TEAEs of diabetic retinopathy or maculopathy (see Section 4.6.2.1.7):

Amaurosis
Amaurosis fugax
Arteriosclerotic retinopathy
Blindness
Blindness transient
Blindness unilateral
Choroidal neovascularisation
Cystoid macular oedema
Detachment of macular retinal pigment epithelium
Detachment of retinal pigment epithelium
Diabetic blindness
Diabetic eye disease
Diabetic retinal oedema

- Diabetic retinopathy
- Diabetic uveitis
- Diplopia
- Exudative retinopathy
- Eye laser surgery
- Fundoscopy
- Fundoscopy abnormal
- Intra-ocular injection
- Macular detachment
- Macular oedema
- Maculopathy
- Noninfective chorioretinitis
- Noninfective retinitis
- Phacotrabeculectomy
- Retinal aneurysm
- Retinal arteriovenous malformation
- Retinal artery embolism
- Retinal artery occlusion
- Retinal artery stenosis
- Retinal collateral vessels
- Retinal cryoablation
- Retinal detachment
- Retinal exudates
- Retinal haemorrhage
- Retinal laser coagulation
- Retinal neovascularisation
- Retinal oedema
- Retinal operation
- Retinal thickening
- Retinal vascular disorder
- Retinal vascular occlusion
- Retinal vein occlusion
- Retinitis
- Retinopathy
- Retinopathy haemorrhagic
- Retinopathy hypertensive
- Retinopathy hyperviscosity
- Retinopathy proliferative
- Scintillating scotoma
- Sudden visual loss
- Venous stasis retinopathy
- Vision blurred
- Visual acuity reduced
- Visual acuity reduced transiently
- Visual impairment
- Vitrectomy

6.8. Appendix 8: MedDRA PT for Peripheral Edema

The analysis of peripheral edema (Section 4.6.2.1.8) will be based on the TEAEs in the following terms:

- Acute pulmonary oedema
- Ascites
- Brain oedema
- Bronchial oedema
- Capillary leak syndrome
- Cerebral oedema management
- Compression garment application
- Cytotoxic oedema
- Effusion
- Fluid retention
- Gastrointestinal oedema
- Generalised oedema
- Gravitational oedema
- Hydraemia
- Hypervolaemia
- Hypoosmolar state
- Lipoedema
- Lymphoedema
- Negative pressure pulmonary oedema
- Non-cardiogenic pulmonary oedema
- Non-pitting oedema
- Oedema
- Oedema blister
- Oedema due to cardiac disease
- Oedema due to hepatic disease
- Oedema due to renal disease
- Oedema mucosal
- Oedema peripheral
- Pelvic fluid collection
- Pericardial effusion
- Perinephric collection
- Perinephric oedema
- Peripheral swelling
- Pleural effusion
- Pulmonary oedema
- Retroperitoneal effusion
- Retroperitoneal oedema
- Skin oedema
- Skin swelling
- Subdural effusion
- Swelling
- Visceral oedema

6.9. Appendix 9: Empirical Estimation of Relative Event Rate

Traditionally, Poisson distribution has been assumed to draw inference for the rate of rare events. When the event is rare and the sample size is large, it is known that the overall number of events is approximately from Poisson distribution. However, for some not very rare events such as severe hypoglycemic events in T2D patients, the total number of events may not be distributed from Poisson and may be over-dispersed. Assuming Poisson distribution may significantly underestimate the variance, and therefore may reduce the overage probability and inflate the Type-I error. An empirical method in estimating the variance of the relative event rate without assuming any distribution on the number of events will be provided in this appendix.

Let X_{ij} denote the count response variable for patient *j* in treatment group *i*. Let $Y_i = \sum_j X_{ij}$ be the total number of events for treatment group *i*, and T_i denote the exposure for treatment group *i*. Let *i* = 0 for the control group and *i* = 1 for the experimental treatment group. The event rate for treatment group *i* can be calculated as:

$$\hat{r}_i = \frac{Y_i}{T_i}$$

The empirical variance of $\hat{r}_i$ is:

$$\widehat{Var}(\hat{r}_i) = T_i^{-2}\widehat{Var}(Y_i) = T_i^{-2} n_i S_i^2,$$

where S_i^2 is the variance of X_{ij} for treatment group *i*. Using the delta-method, the variance of $\log(\hat{r}_i)$ can be estimated as:

$$\widehat{Var}(\log(\hat{r}_i)) = Y_i^{-2} n_i S_i^2$$

The relative rate of the experimental treatment versus the control treatment is estimated as:

$$\hat{\lambda} = \frac{\hat{r}_1}{\hat{r}_0}$$

The variances of $\hat{\lambda}$ and $\log(\hat{\lambda})$ are:

$$\widehat{Var}(\hat{\lambda}) = \hat{\lambda}^2 \widehat{Var}(\log(\hat{\lambda}))$$

$$\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right) = \widehat{Var}(\log(\hat{r}_0)) + \widehat{Var}(\log(\hat{r}_1)) = Y_0^{-2} n_0 S_0^2 + Y_1^{-2} n_1 S_1^2$$

Assuming $\log(\hat{\lambda})$ is asymptotically from a normal distribution, the $100(1-\alpha)\%$ confidence interval for $\log(\hat{\lambda})$ can be constructed as:

$$\left[\log\left(\hat{\lambda}\right) - z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}, \log\left(\hat{\lambda}\right) + z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}\right]$$

Then, the $100(1-\alpha)\%$ confidence interval for $\hat{\lambda}$ is:

$$\left[\hat{\lambda}\exp\left(-z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}\right), \quad \hat{\lambda}\exp\left(z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}\right)\right] \tag{1}$$

The p-value for testing the null hypothesis of $H_0: \lambda = 1$ is calculated as:

$$p = 2\Phi\left(\left|\log(\hat{\lambda})\right| / \sqrt{\widehat{Var}(\log(\hat{\lambda}))}\right) \quad (2)$$

6.10. Appendix 10: Definition for Persistent-Recurrent Hypoglycemia

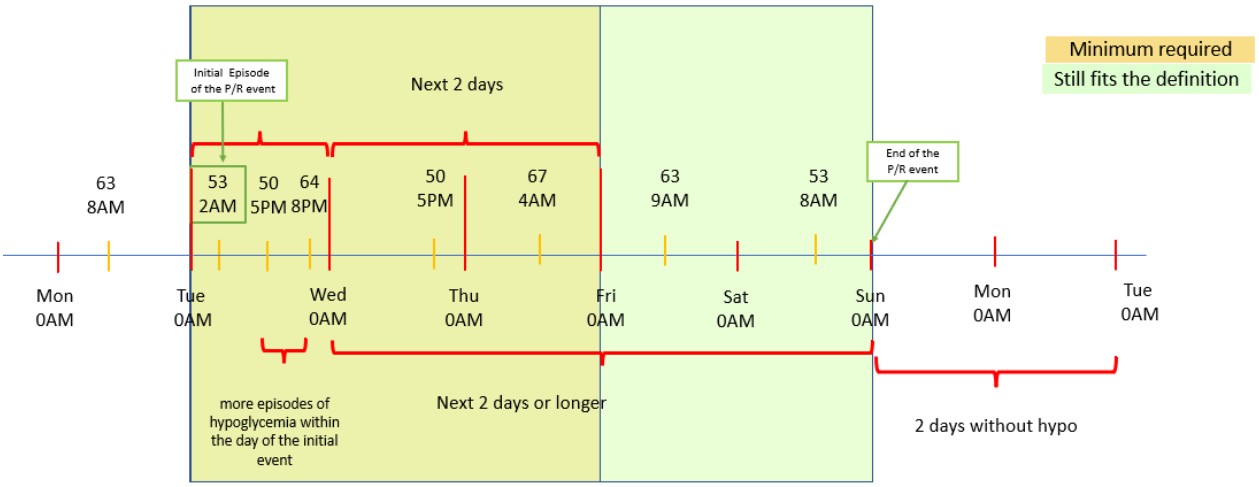
A P-R hypoglycemia based on programming search in the e-diary database for hypoglycemic events that meet prespecified criteria is defined as a set of hypoglycemic episodes that:

a) starts with the occurrence of a level 3 or level 2 hypoglycemic episode (<54mg/dL, [3.0 mmol/L]) and is followed by more episodes of hypoglycemia (<70mg/dL, [3.9 mmol/L]), within the day of the initial episode,

AND

b) is followed by at least one episode of hypoglycemia (<70mg/dL, [3.9 mmol/L]) per day, in the next 2 days or longer, and that ends when no hypoglycemia episode occurs for at least 2 days.

An example of a set of hypoglycemic episodes meeting the prespecified criteria for a P-R hypoglycemia event is illustrated in the figure below.



6.11. Appendix 11: Abnormality Level Criteria for Chemistry and Hematology Laboratory Results

Parameter	Level 1	Level 2	Level 3
General Chemistry			
Sodium, low (mEq/L)	<132	<130	<125
Sodium, high (mEq/L)	>150	>155	>160
Potassium, low (mEq/L)	<3.6	<3.4	<3.0
Potassium, high (mEq/L)	>5.5	>6	>6.5
Chloride, low (mEq/L)	<95	<88	<80
Chloride, high (mEq/L)	>108	>112	>115
Bicarbonate, low (mEq/L)	<20	<18	<15
Bicarbonate, high (mEq/L)	N/A	N/A	>30
Blood urea nitrogen, high (mg/dL)	>23	>27	>31
Calcium, low (mg/dL)	<8.4	<8.0	<7.5
Calcium, high (mg/dL)	>10.5	>11.0	>12.0
Phosphate, low (mg/dL)	<2.5	<2.0	<1.4
Protein (total), low (g/dL)	<6.0	<5.4	<5.0
Albumin, low (g/dL)	<3.1	<2.5	<2.0
Uric Acid (urate), high (mg/dL)	>7.0	NA	NA
Kidney Function			
Creatinine, increase (mg/dL)	≥1.5 × baseline	≥2.0 × baseline	≥3.0 × baseline
eGFR, decrease (mL/min/1.73m^2)	≥25% decrease	≥50% decrease	≥75% decrease
Lipids			
Cholesterol (total), high (mg/dL)	>200	>240	>300
HDL, low (mg/dL), males	<40	<30	<20
HDL, low (mg/dL), females	<50	<40	<20
LDL, high (mg/dL)	>130	>160	>190
Triglycerides, high (mg/dL)	>150	>300	>500
Hematology			
Complete Blood Count			
WBC, low (cells/µL)	<3500	<3000	<1000
WBC, high (cells/µL)	>10,800	>13,000	>15,000
Hemoglobin, decrease (g/dL)	N/A	>1.5 dec. from baseline	>2 dec. from baseline
Hemoglobin, increase (g/dL)	N/A	>2 inc. from baseline	>3 inc. from baseline
Platelets, low (cells/µL)	<140,000	<125,000	<100,000
Hemoglobin, low (g/dL), male	12.5-13.5	<12.5	<10.5
Hemoglobin, low (g/dL), female	11.0 – 12.0	<11	<9.5
WBC Differential			
Lymphocytes, low (cells/µL)	<1000	<750	<500
Lymphocytes, high (cells/µL)	>4000	>10,000	>20,000
Neutrophils, low (cells/µL)	<2000	<1000	<500
Eosinophils, high (cells/µL)	>650	>1500	>5000

Parameter	Level 1	Level 2	Level 3
Coagulation Studies			
Prothrombin time, increase (sec)	>1.1 × ULN	>1.3 × ULN	>1.5 × ULN

Abbreviations: eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; WBC = white blood cell.

Note: For liver enzymes, Lilly defined categories will be used.

6.12. Appendix 12: Interaction Effect for Subgroup Analysis – Treatment Regimen Estimand

The ANCOVA analysis will be performed within each subgroup with multiple imputation of missing primary measures. Statistical inference over multiple imputation of missing data will be guided by Rubin (1987) to obtain $\hat{\theta}_1$ and $se(\hat{\theta}_1)$ for the treatment difference in subgroup 1, and $\hat{\theta}_2$ and $se(\hat{\theta}_2)$ in subgroup 2. Then, the distribution of treatment by subgroup interaction (difference of treatment effects) is: $\hat{\theta}_1 - \hat{\theta}_2 \sim N\left(\theta_1 - \theta_2\ , \left[se(\hat{\theta}_1)\right]^2 + \left[se(\hat{\theta}_2)\right]^2\right)$

A z-statistic can be contrasted such that $z = \frac{\hat{\theta}_1 - \hat{\theta}_2}{\sqrt{\left[se(\hat{\theta}_1)\right]^2 + \left[se(\hat{\theta}_2)\right]^2}} \sim N(0,1)$, under the null hypothesis of no treatment by subgroup interaction.

For more than 2 groups (k groups),

let $\hat{\boldsymbol{\theta}} = \left(\hat{\theta}_1\ , \hat{\theta}_2\ , \ldots , \hat{\theta}_k\right)$ and $Var\left(\hat{\boldsymbol{\theta}}\right) = diag\left(\left[se(\hat{\theta}_1)\right]^2, \left[se(\hat{\theta}_2)\right]^2, \ldots , \left[se(\hat{\theta}_k)\right]^2\right)$.

A chi-square test (df=k-1) can be constructed as

$$T = \left(C\hat{\boldsymbol{\theta}}\right)'(CVC')^{-1}\left(C\hat{\boldsymbol{\theta}}\right) \sim \chi^2_{k-1}$$

where C is a matrix of contrast such that

$$C = \begin{bmatrix} -1 & 1 & 0 & \ldots & 0 & 0 \\ 0 & -1 & 1 & \ldots & 0 & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & 0 & \ldots & -1 & 1 \end{bmatrix}.$$

6.13. Appendix 13: Statistical Analysis for China

Separate analyses will be performed for participants participating in Study BDCX from China.

The analysis methods will be similar to those described for the main study.

The analyses to be included will be documented in a separate list of analyses.

6.14. Appendix 14: Statistical Analysis for Japan

Separate analyses will be performed for participants participating in Study BDCX from Japan based on following subpopulations:

- Japanese population,
- Japanese population who **chose** initial loading dose of 150 U for LY3209590 **or** 5U for Degludec based on the I8H-MC-BDCX protocol addendum (2), and
- Japanese population who **did not choose** initial loading dose of 150 U for LY3209590 **or** 5U for Degludec based on the I8H-MC-BDCX protocol addendum (2).

The analysis methods will be similar to those described for the main part of this statistical analysis plan. If there is not sufficient number of participants in the subpopulation, summary statistics will be provided instead. Efficacy analyses for Japan will be based on efficacy estimand. In addition, Asian subgroup analyses may also be performed.

The analyses to be included will be documented in a separate list of analyses which should include dispositions, demographics, and selected efficacy and safety endpoints.

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