Statistical Analysis Plan I8H-MC-BDCY Version 3

A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared With Insulin Degludec in Participants With Type 1 Diabetes Treated With Multiple Daily Injection Therapy

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Title Page

Protocol Title: A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

Protocol Number: I8H-MC-BDCY

Compound Number: LY3209590

Short Title: Efficacy and Safety of LY3209590 Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

Acronym: QWINT-5

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

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Version History

This Statistical Analysis Plan (SAP) for Study I8H-MC-BDCY (BDCY) is the third version and was approved prior to the final database lock. The first version of SAP BDCY was approved prior to the first participant visit. The SAP versions are based on the Protocol, Protocol Amendment (a), Protocol Amendment (b), and Protocol Amendment (c), approved on 08 March 2022, 10 May 2022, 21 June 2022, and 12 October 2022 respectively, and Japan Addendum 2.1, approved on 10 May 2022.

Table BDCY.1.1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	01 June 2022	Not applicable	Original version
2	20 January 2024	Added, in Section 2.1, the plan for multiplicity adjustment for primary and key secondary efficacy objectives – the details of type 1 error control strategy.	To finalize the multiplicity adjustment strategy.
		Edited Section 3, to adjust Efficacy Analysis Set 2 for Efficacy Estimand.	To redefine the cut-off for different analysis and intercurrent events.
		Edited Section 4.1 to update the definitions of baseline and post-baseline observations for different analysis.	For clarity and consistency with data collection.
		Added, in Section 4.2, analysis of time-to-event of interest in disposition.	To align with PSAP.
		Edited Section 4.3.3 for sensitivity analysis of primary endpoint and added Section 4.4.1.3 for sensitivity analysis of key secondary endpoints.	To address regulatory feedback.
		Added subsections to Section 4.4.2.	For clarification of each supportive secondary endpoints.
		Added subsections in Section 4.5.1 to explicitly mention analysis method for tertiary outcome measures. Methodology for multiple imputations for missing data have been updated.	To address regulatory feedback.
		Changes were made throughout Section 4.6.2 1. for laboratory analysis, removed shift analysis, treatment-emergent high/low and add elevated or low values meeting specified levels, and 2. risk difference, odds ratio and 95% will be used for safety categorical data analysis.	To align with PSAP.
		Added Section 4.6.3.1.2 for analysis for CGM-based hypoglycemic events.	Per CGM international consensus statement.

SAP Version	Approval Date	Change	Rationale
		Edited Section 4.7.1 and Section 4.7.2 for clarification and reorganizing of the corresponding analyses. Hence, added Section 6.12 to clarify the interaction effect for subgroup analysis.	For clarity.
		Edited and added texts in Section 6.6 to clarify handling of missing CGM data and definitions of CGM derived hypoglycemic episodes.	Per CGM international consensus statement 2023.
		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 the SAP made minor changes and reorganization.	For clarity, no change to analysis methodologies, so not detailed.
3	Prior to the database lock	Added treatment regimen analysis for the selected secondary and tertiary endpoints (fasting serum glucose, fasting glucose from SMBG), and selected CGM parameters in Sections 4.1 and 4.4.2.1.	To implement FDA feedback.
		Added missing data at baseline which will be imputed using MI approach under MAR assumption in Section 4.4.1.	Addition.
		Modified missing data handling approach for hypoglycemia in the composite endpoints of HbA1c and hypoglycemia in Section 4.5.1.	To implement FDA feedback.
		Updated the estimator of logistic regression for binary outcomes with unconditional treatment group effect for binary endpoints and also to include interaction terms for composite endpoints in Section 4.5.1.	To implement FDA feedback.
		Updated the HbA1c composite endpoint from no nocturnal level 2/3 hypoglycemia to no nocturnal level 2 hypoglycemia as originally stated in SAP version 1 of Section 4.5.1.	To rectify the inadvertently updated HbA1c composite endpoint.
		Added Section 4.6.3.1.1.1 sensitivity analysis that considers all hypoglycemic events as one hypoglycemic event until a succeeding glucose value is ≥70 mg/dL.	To implement FDA feedback from BDCV SAP.
		Added Section 4.6.4 analysis for device product complaints.	To align with the new SAP template requirement.
		Updated the subgroups for race in Section 4.7.2.	To implement FDA feedback.

SAP Version	Approval Date	Change	Rationale
		Clarified definitions of valid CGM period and visit; added sensitivity analysis for selected CGM parameters that derived from all data in Appendix 6.	To implement FDA feedback.
		Added subgroup analysis for age <65 years and ≥65 years in Section 4.7.2.	To implement FDA feedback.
		Clarified the SAP language regarding the use unplanned measurements for post-baseline observations for HbA1c analysis in Section 4.1.	To clarify FDA feedback.
		Clarified the SAP language for sensitivity analysis in Section 4.3.3.1.	To clarify FDA feedback.

Abbreviations: CGM = continuous glucose monitoring; HbA1c = glycated hemoglobin; MAR = missing at random; ME2 = maximum extended enrollment; MI = multiple imputation; PSAP = program safety analysis plan, SAP = statistical analysis plan; SMBG = self-monitored blood glucose.

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 analysis details for efficacy, safety measures, patient-reported outcomes, and parameters based on continuous glucose monitoring (CGM). The analysis described in this SAP is primarily for the Clinical Study Report (CSR). Additional analysis will also be done for the Summary of Clinical Safety related to the Type 1 diabetes mellitus (T1D) indication. Details regarding these additional analyses are outlined in the Program Safety Analysis Plan (PSAP). Pharmacokinetic/pharmacodynamic (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	
• To demonstrate that LY3209590 is noninferior to insulin degludec for the treatment of T1D in adults	• Change in HbA1c from baseline to Week 26
Key Secondary (Multiplicity Adjusted)	
• To demonstrate superiority of LY3209590 to insulin degludec	• Change in HbA1c from baseline to Week 26 • Time in glucose range between 70-180 mg/dL (3.9-10.0 mmol/L), inclusive, measured by CGM 4 weeks prior to Week 26 • Event rate of participant-reported, clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during the treatment phase up to Week 52
Other Secondary	
• To investigate the effect of LY3209590 compared with insulin degludec in additional parameters of glycemic control	• Change in HbA1c from baseline to Week 52 • Change from baseline to Weeks 26 and 52 in fasting glucose as measured by SMBG • Glucose variability, measured by CGM 4 weeks prior to Weeks 26 and 52

Objectives	Endpoints

	• Time in glucose range between 70-180 mg/dL (3.9-10.0 mmol/L), inclusive, measured by CGM 4 weeks prior to Week 52
	• Insulin dose at Weeks 26 and 52
	  o basal
	  o bolus
	  o total, and
	  o basal/total insulin dose ratio

• To compare the safety of LY3209590 to insulin degludec	• Rate of composite of Level 2 and 3 hypoglycemia events during the treatment period • Body weight change from baseline to Weeks 26 and 52 • Time in hypoglycemia range with glucose <54 mg/dL (3.0 mmol/L), measured by CGM 4 weeks prior to Weeks 26 and 52 • Time in hyperglycemia range, defined as glucose >180 mg/dL (10.0 mmol/L), measured by CGM 4 weeks prior to Weeks 26 and 52
• To compare treatment satisfaction and health-related quality of life between LY3209590 and degludec as assessed by patient-reported outcome questionnaires	• DTSQ change from baseline to Weeks 26 and 52 • Change in SF-36 v2 acute form domain scores from baseline to Weeks 26 and 52
Tertiary	
• To investigate the effect of LY3209590 compared with insulin degludec on other measures of efficacy, safety, and patient-reported outcomes	Efficacy • Percentage of participants achieving HbA1c <7% at Weeks 26 and 52 • Percentage of participants achieving HbA1c ≤6.5% at Weeks 26 and 52 • Change from baseline to Weeks 26 and 52 in fasting serum glucose as measured by a central laboratory

Objectives	Endpoints
	Safety • Rate and incidence of Level 2 hypoglycemia events during the treatment period • Rate and incidence of Level 3 hypoglycemia events during the treatment period • Incidence of positive treatment-emergent antibodies of LY3209590
	Patient-reported outcomes • Frequency of responses to "Basal Insulin Experience: Likelihood of incorporating into routine" at Weeks 26 and 52 • Frequency of responses to "Basal Insulin Experience: Preference" at Weeks 26 and 52 • Change in EQ-5D-5L from baseline to Weeks 26 and 52
To characterize the PK/PD of LY3209590	• LY3209590 PK and concentration response relationships to key safety and efficacy measures. • Potential intrinsic and extrinsic factors.

Abbreviations: CGM = continuous glucose monitoring; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D-5L = European Quality of Life Questionnaire; HbA1c = hemoglobin A1c; PK/PD = pharmacokinetics/pharmacodynamics; SF-36 v2 = Short Form-36 Version 2 Health Survey Acute Form; SMBG = self-monitored blood glucose; T1D = Type 1 diabetes mellitus.

Primary estimand (for primary objective)

United States registration

The *primary* clinical question of interest is below:

- What is the treatment difference between LY3209590 and insulin degludec in hemoglobin A1c (HbA1c) change from baseline after 26 weeks of treatment, in study-eligible participants with T1D treated with multiple daily injection (MDI) therapy, 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 Attributes	Description
Population	Targeted study population. See Section 3 for details.
Endpoint	HbA1c change from baseline to Week 26.
Remaining intercurrent events	None. The intercurrent events, treatment discontinuation for any reason, and initiation of rescue medication, are 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.

Abbreviation: HbA1c = hemoglobin A1c.

Rationale for the treatment-regimen estimand

The treatment-regimen estimand estimates how participants with T1D 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 below:

- What is the treatment difference between LY3209590 and insulin degludec in hemoglobin A1c (HbA1c) change from baseline after 26 weeks of treatment, in study-eligible participants with T1D treated with MDI therapy who adhere to the randomized treatment without an intercurrent event 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	Hemoglobin A1c change from baseline to Week 26.
Remaining intercurrent event	None. The intercurrent event, treatment discontinuation for any reason, and initiation of rescue medication, are addressed 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.

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

Secondary estimands for multiplicity-adjusted objectives

The superiority test in change from baseline to Week 26 (Visit 22) in HbA1c will also be based on the primary estimand described above.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, measured by continuous glucose monitoring (CGM) in the 4 weeks prior to Visit 22 (Week 26) will use the treatment regimen estimated for US registration and the efficacy estimand for other countries.

Participant-reported, clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) is one of the safety measures for the study. The event rate will be based on all available data during the specific analysis period. The relative rate between randomized treatment groups will be used for treatment comparison.

1.2. Study Design

- Study BDCY is a Phase 3, open-label, 2-arm, parallel-design, randomized control study to investigate if LY3209590 is noninferior to insulin degludec in adult participants with T1D who are treated with basal-bolus insulin MDI therapy.
- This study consists of a 1-week screening period, a 2-week lead-in period, a 52-week treatment period, and a 5-week safety follow-up period.
- Participants will be randomly assigned in a 1:1 ratio to LY3209590:insulin degludec. All participants will be treated with basal-bolus MDI therapy, which will be titrated to glycemic targets and as clinically indicated for hyperglycemia.
- Participants will be stratified based on country, HbA1c stratum (<8% and ≥8%) at screening Visit 1, CGM use prior to study entry (yes/no), and carbohydrate counting for prandial insulin dosing (yes/no).
- 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.

2. Statistical Hypotheses

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 in HbA1c from baseline to Week 26 (Visit 22) in adults with T1D currently on basal-bolus insulin MDI therapy.

The null hypothesis ($H_{1,0}$) is the difference between LY3209590 and insulin degludec in the change in HbA1c from baseline to Week 26 (Visit 22) is greater than the noninferiority margin (NIM).

The NIMs of 0.4% and 0.3% will both be tested to meet different regulatory requirements. A 2-sided 95% confidence interval (CI) will be used for testing noninferiority.

Secondary hypotheses

The key secondary (multiplicity adjusted) objectives are to test the hypotheses that LY3209590 is superior to insulin degludec with respect to

- change in HbA1c from baseline to Week 26 (Visit 22)
  - $H_{2,0}$: the difference (LY3209590 - insulin degludec) ≥0.0
- time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, measured by CGM 4 weeks prior to Week 26 (Visit 22)
  - $H_{3,0}$: the difference (LY3209590 - insulin degludec) ≤0.0, and
- the event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during the treatment period up to Week 52 (Visit 29)
  - $H_{4,0}$: the relative event rate (LY3209590 versus insulin degludec) ≥1.

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 1 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 noninferiority will be achieved, and the α of 0.05 will be distributed to test superiority 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 superiority 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 successful. The NIM of 0.4% (for the treatment regimen estimand) and 0.3% (for the 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 the type 1 error control strategy are illustrated in Figure BDCY.2.1. No multiplicity adjustments will be made for evaluating other secondary and exploratory objectives, or for safety assessments.

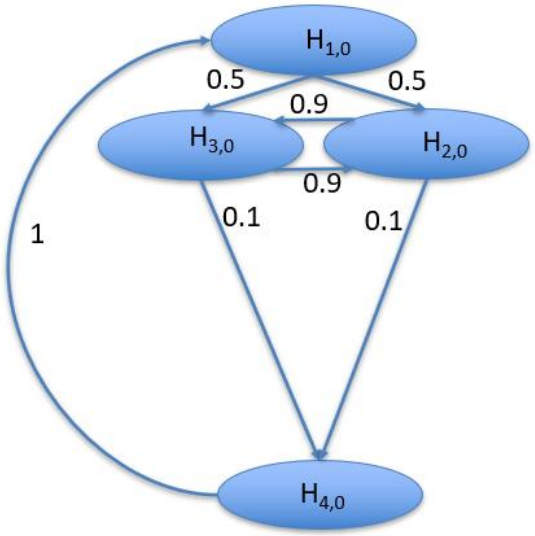

Figure BDCY.2.1. Type 1 error control strategy for primary and key secondary efficacy endpoints.

3. Analysis Sets

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

Analysis Populations/ Datasets	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 LY3209590 or insulin degludec. Participants will be analyzed according to the treatment they were assigned.
Efficacy Analysis Set 1 (EAS1) for the treatment-regimen estimand	The data will include • the 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 the efficacy estimand on efficacy measures	The data will include • the 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 the dates below for individual participants other than the analysis on study dose: • the date of last study dose + 10 days for LY3209590, or +1 day for degludec • 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 • the start date of the first rescue medication
Safety Analysis Set (SS)	The data will include • the mITT population, and • all measurements, regardless of the use of study treatment or rescue medications

Approved on 22 May 2024 GMT

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (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. Statistical analyses for Japan Addendum are described in Appendix 12 (Section 6.13).

Unless otherwise stated, the efficacy analyses will be based on either Efficacy Analysis Set 1 (EAS1, see the definition in Section 3) or Efficacy Analysis Set 2 (EAS2, see the definition in Section 3). For the treatment-regimen estimand, EAS1 will be used. Unless otherwise specified, for the efficacy estimand, other secondary, and tertiary efficacy measures, EAS2 will be used. The treatment comparison will be based on either the 2-sided test or 95% CI.

Unless otherwise noted, the safety analyses will be conducted on the Safety Analysis Set (SS; see the definition in Section 3). Percentages will be calculated using the modified intent-to-treat (mITT) 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.

For continuous measures, summary statistics will include sample size, mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. For certain variables that are considered to be log-normally distributed, the geometric mean and coefficient of variation (CV) will be provided instead. Either a mixed model for repeated measures (MMRM) model or an analysis of covariance (ANCOVA) model will be used to analyze continuous outcomes. Least-squares (LS) means and standard errors (SEs) 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, negative binomial regression will be used to analyze the number of hypoglycemic episodes. Group mean, instead of LS mean, will be estimated, and the delta method will be used to estimate the SE 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 group mean is that the 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 severe hypoglycemia, the empirical

method, based on exposure-adjusted rate (calculated by the total number of events divided by total exposure), may be used for treatment comparison if the number of episodes is too small and leads to convergency issues in the negative binomial regression model.

The table below describes the definition of baseline and postbaseline observations for different analyses.

Analysis	Baseline Observations	Postbaseline Observations
HbA1c (treatment-regimen estimand)	Baseline is the last non-missing assessment prior to or on the day of first dose of study treatment.	Planned measurements at Week 26 (primary endpoint, Visit 22) and Week 52 (secondary endpoint, Visit 29) in EAS1. Use unplanned measurements (on the same visit day) if there are no planned measurements. A multiple imputation approach will be used to impute missing observations at Week 26 (Visit 22) and Week 52 (Visit 29).
HbA1c (efficacy estimand)	Baseline is the last non-missing assessment prior to or on the day of first dose of study.	Weeks 2, 4, 12, 16, 26, 36, and 52 (Visits 5, 7, 15, 17, 22, 25, and 29) in EAS2 for MMRM. All planned measurements at scheduled visits will be included. Use unplanned measurements (on the same visit day) if there are no planned measurements.
CGM parameters (treatment-regimen estimand)	Baseline will be derived from the data collected prior to the first dose of study treatment. A multiple imputation will be used to impute missing observations at baseline.	The CGM values 4 weeks prior to Week 26 (Visit 22) and Week 52 (Visit 29) in EAS1. A multiple imputation approach will be used to impute missing observations at Week 26 (Visit 22) and Week 52 (Visit 29). See detailed derivations in Appendix 6 (Section 6.6).
CGM parameters (efficacy estimand)	Baseline will be derived from the data collected prior to the first dose of study treatment.	The CGM values prior to Weeks 4, 8, 12, 16, 22, 26, 32, 36, 40, 44, 48, and 52 (Visits 7, 11, 15, 17, 20, 22, 24, 25, 26, 27, 28, and 29) in EAS2 for MMRM. See detailed derivations in Appendix 6 (Section 6.6).
Basal insulin dose	The baseline period is the screening/lead-in period prior to the initiation of study treatment. The following variables will be derived: • daily dose in U • weekly dose in U, and • dose in U/kg/day. See a detailed derivation of variables in Section 4.4.2.1.	All scheduled visits between Week 0 (Visit 3) and Week 52 (Visit 29) in EAS2 for MMRM. The following variables will be derived: • daily dose in U • weekly dose in U, and • dose in U/kg/day See a detailed derivation of variables in Section 4.4.2.1.

Analysis	Baseline Observations	Postbaseline Observations
Prandial (bolus) insulin dose	The baseline period is the screening/lead-in period prior to the initiation of study treatment. The following variables will be derived: • daily dose in U • weekly dose in U, and • dose in U/kg/day. See a detailed derivation of variables in Section 4.4.2.1.	All scheduled visits after Week 0 (Visit 3) and up to Week 52 (Visit 29) in EAS2 for MMRM The following variables will be derived: • daily dose in U • weekly dose in U, and • dose in U/kg/day See a detailed derivation of variables in Section 4.4.2.1.
Total insulin dose	The baseline period is the screening/lead-in period prior to the initiation of study treatment. The following variables will be derived: • daily dose in U • weekly dose in U, and • dose in U/kg/day. See a detailed derivation of variables in Section 4.4.2.1.	All scheduled visits after Week 0 (Visit 3) and up to Week 52 (Visit 29) in EAS2 for MMRM The following variables will be derived: • daily dose in U • weekly dose in U, and • dose in U/kg/day. See a detailed derivation of variables in Section 4.4.2.1.
Basal/total insulin dose ratio	The baseline period is the screening/lead-in period prior to the initiation of study treatment. See a detailed derivation of variables in Section 4.4.2.1.	All scheduled visits after Week 0 (Visit 3) and up to Week 52 (Visit 29) in EAS2 for MMRM See a detailed derivation of variables in 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 the Visit 2 date and the first dose date. For treatment regimen estimand, multiple imputation will be used to impute missing observations at baseline.	For efficacy estimand, all available data from the day of first dose of study treatment up to Week 52 (Visit 29) in EAS2 for MMRM. Values at each visit will be derived as the average of all fasting glucose measurements from the day post the prior visit up to the day of the visit. For treatment regimen estimand data at Week 26 (Visit 22) and Week 52 (Visit 29) in EAS1 for ANCOVA with multiple imputation for missing data.

Analysis	Baseline Observations	Postbaseline Observations
Fasting serum glucose	The baseline is the last non-missing assessment prior to or on the day of the first dose of study treatment. For treatment regimen estimand, multiple imputation will be used to impute missing observations at baseline.	All planned measurements at scheduled visits will be included. Use unplanned measurements (on the same visit day) if there are no planned measurements. For efficacy estimand, all scheduled visits after the day of first dose of study treatment up to Week 52 (Visit 29) in EAS2 for MMRM. For treatment regimen estimand, data at Week 26 (Visit 24) and Week 52 (Visit 31) in EAS1 for ANCOVA with multiple imputation for missing data.
Participant-reported hypoglycemia	The baseline period is the screening/lead-in period prior to the first dose of study treatment.	• The treatment period starts on or after the first dose of study treatment and ends at Week 52 (Visit 29) if completed treatment, or on the last dose date of study treatment + 10 days for LY3209590, +1 day for degludec if discontinued study treatment early • The posttreatment period starts from Week 52 (Visit 29) + 1 day if completed treatment, or the 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 (AE Start Relative to Exposure Assessment in CRF is used to determine).	The safety-analysis period starts after the first dose and ends at the last visit in the study, including the safety follow-up period.
Safety laboratory tests, vital signs, and body weight	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 Week 52 (Visit 29) for MMRM Planned measurements at scheduled visits will be included.

Analysis	Baseline Observations	Postbaseline Observations
Laboratory values elevated or low, vital signs, and body weight categorical measures	Starts from the screening visit and ends prior to or on the first dose date of the 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 the treatment period and follow-up period. All available measurements at scheduled and unscheduled visits in the specified analysis period will be included.
Anti-LY3209590 antibodies	Refer to PSAP	Refer to PSAP
Patient-reported outcomes	Baseline will be the data collected at Visit 3.	• All scheduled visits after Week 0 (Visit 3) • Last collection after Week 0 (Visit 3)

Abbreviations: AE = adverse event; CGM = continuous glucose monitoring; CRF = case report form; EAS1 = Efficacy Analysis Set 1; EAS2 = Efficacy Analysis Set 2; HbA1c = hemoglobin A1c; MMRM = mixed model of repeated measures; PSAP = Program Safety Analysis Plan; SMBG = self-monitored blood glucose; 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 but have not been randomized.

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 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 adverse events (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 26 (Visit 22). The HbA1c is reported in unit of percentage by central laboratory and will be converted to the unit of mmol/mol using the following formula:

$$HbA1c\ in\ mmol/mol = 10.93 \times HbA1c\ in\ \% - 23.5\ (NGSP\ 2010).$$

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.

This table provides the details of treatment-regimen estimand and efficacy estimand.

	Treatment-Regimen Estimand	**Efficacy Estimand**
Analysis Population	All participants in EAS1 with a non-missing baseline measure.	All participants in EAS2 with a non-missing baseline measure and at least 1 non-missing postbaseline scheduled measure.
Analysis Data	All non-missing observations at baseline and Week 26 (Visit 22) regardless of the use of study intervention or rescue medications.	All non-missing observations at baseline and all scheduled postbaseline timepoints during the treatment period (that is, Weeks 2, 4, 12, 16, 26, 36, and 52) (prior to the date of the 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 26 (Visit 22) 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 26 but have non-missing measures at Week 26. If there is only a limited number of retrieved participants (that is, at least 1 arm has <8 participants who discontinued study treatment early and have endpoint visit measurements) or the model cannot converge, the missing HbA1c at Week 26 will be imputed by return-to-baseline multiple imputation approach[a].	There may be missing values due to the early discontinuation of the study intervention or use of rescue medication. The MMRM model will be used, and the missing values will be handled implicitly 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, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), and baseline value of the dependent variable as independent variables. The statistical inference will be based on the multiple imputation framework by Rubin[b].	The MMRM model will include treatment, strata (country, baseline, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), and 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, and 6. compound symmetry without heterogeneous variances.

Abbreviations: ANCOVA = analysis of covariance; CGM = continuous glucose monitoring; EAS1 = Efficacy Analysis Set 1; HbA1c = hemoglobin A1c; EAS2 = Efficacy Analysis Set 2; MMRM = mixed model of repeated measures.

[a] (Qu and Dai 2022)

[b] (Rubin 1987)

The 2-sided 95% CI of the LS mean difference (LY3209590 - insulin degludec) in the HbA1c change from baseline to Week 26 (Visit 22) 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 the 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 in treatment regimen estimand, a 2-way tipping point analysis 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. Penalties for imputed missing values will be added for both treatment arms. The ANCOVA model for treatment regimen estimand will be conducted after the penalties are added. The multiple imputation framework by Rubin (1987) will be used to summarize the results. The corresponding p-value of the noninferiority test will be shown by color scale in the figure.

Additionally, after imputing the missing data used in the treatment-regimen estimand (Section 4.3.2), imputation under the noninferiority null hypothesis will be conducted by adding 0.4 (NIM) to the same imputed data for the LY3209590 group only. The ANCOVA model for the treatment-regimen estimand will be 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 the mITT population, including inadvertently enrolled participants, for both treatment regimen estimand and efficacy estimand.

4.3.4. Supplementary Analyses

Additional analysis may be conducted as needed.

4.4. Secondary Endpoint Analysis

4.4.1. Key Secondary Endpoints

A graphical approach (Bertz et al. 2009, 2011) will be used to control the overall type 1 error for the primary objective and test the superiority of LY3209590 compared with insulin degludec for

1) change from baseline in HbA1c at Week 26 (Visit 22)
2) time in glucose range between 70 and 180 mg/dL, inclusive, measured by CGM 4 weeks prior to Week 26 (Visit 22), and
3) the event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL or severe) during the treatment phase up to Week 52 (Visit 29).

4.4.1.1. Definition of Endpoint(s)

See Section 4.3.1 for HbA1c change from baseline to Week 26 (Visit 22).

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 in the 4 weeks prior to Week 26. The derivation of CGM parameters is provided in Appendix 6 (Section 6.6).

The hypoglycemia events will be based on participant entry into an electronic diary, which receives all blood glucose (BG) measurements performed by the participant and transmits via Bluetooth from the study-provided glucometer. The nocturnal period is defined by midnight to 0600. The event rate of nocturnal hypoglycemia will be based on the count of the hypoglycemia episodes in the clinically significant nocturnal period and the corresponding exposure of study intervention.

4.4.1.2. Main Analytical Approach

The superiority test in change from baseline to Week 26 (Visit 22) 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 the treatment-regimen estimand (using data from EAS1) and an MMRM model for the efficacy estimand (using data from EAS2). 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 the treatment-regimen estimand, only participants with an observation at baseline or at Week 26 (Visit 22) will be included in the analysis. The missing data at baseline will be imputed using multiple imputation with assumption of missing at random. Missing data at Week 26 (Visit 22) will be imputed by multiple imputation with the approach similar to the imputation used for the primary endpoint.

The rate of participant-reported nocturnal hypoglycemia will be analyzed by a negative binomial regression. The analysis details are provided in Section 4.6.3.1.1.

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 inadvertently enrolled participants using mITT population.

4.4.2. Supportive Secondary Endpoints

4.4.2.1. Other Efficacy Endpoints

The analysis of change from baseline for HbA1c at Week 52, fasting glucose by self-monitored blood glucose (SMBG) at Weeks 26 and 52, CGM (except for variability) parameters at Weeks 26 and 52 will be performed for both treatment regimen estimand and efficacy estimand.

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 1 post baseline observation will be included in the analysis. The longitudinal observations of actual and change from baseline in HbA1c up to Week 52 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 (insulin dose, fasting glucose, 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.

Additional analyses are as specified below.

4.4.2.1.1. Analysis for CGM Parameters

The time in glucose ranges will be based on the percentage and time of CGM readings within the glucose ranges, and glucose variability will be based on the readings during the specific CGM period. Appendix 6 (Section 6.6) provides the derivation of CGM parameters.

A longitudinal logistic regression model with independent variables of treatment, strata (country, baseline, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin

dosing [yes/no]), visit and treatment-by-visit interaction and baseline of the dependent variable will be used to analyze the CGM targets of glycemic controls (see Section 6.6.1). The same order mentioned for the MMRM in Section 4.3.2 will be used for the selection of variance-covariance structure.

The time point for primary CGM data analysis is CGM period. 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. The average daily time since last dose by CGM period during treatment period will also be summarized for LY3209590. Missing data patterns will be summarized at daily, weekly (visit), and CGM period levels.

4.4.2.1.2. Study Insulin Dose Analysis

For the study basal insulin dose, both average daily and weekly basal doses between visits in the treatment period for individual participants will be analyzed.

In the LY3209590 group,

- the average weekly dose of each visit (that is, average of weekly doses since the last visit) will be used as the average weekly basal dose, and
- the average daily basal dose will be the average weekly basal dose divided by 7.

For the insulin degludec group,

- the average daily basal dose since the last visit will be computed for each visit, and
- the average weekly basal dose will be calculated as the average daily basal dose multiplied by 7.

For all participants (with the exception of those treated with prestudy basal insulin glargine U-300), the average prestudy basal daily dose during the screening/lead-in period will be the baseline daily basal dose. For participants using prestudy glargine U-300, the average prestudy basal daily dose during the screening/lead-in period, multiplied by 0.8, will be the baseline daily basal dose. The baseline daily basal dose multiplied by 7 will be the baseline weekly basal dose.

The average bolus insulin dose of morning meal, midday meal, evening meal, and daily sum of additional doses between visits will be calculated for individual participants. Then the sum of averages of each visit for individual participants will be the average daily bolus dose. On the first day of study basal insulin (either LY3209590 or insulin degludec), a participant may use both prestudy bolus insulin and study-provided insulin lispro. Therefore, Week 0 (the first day of study basal insulin) will be excluded from the analysis of bolus insulin dose. The average weekly bolus dose is the average daily bolus dose multiplied by 7.

The average weekly total insulin dose is the sum of the average weekly basal dose and average weekly bolus dose. The average daily total insulin dose is the average weekly total insulin dose divided by 7.

The basal/total insulin dose ratio at each visit is the ratio of the average weekly basal dose and the average weekly total insulin dose.

If either weekly basal dose or weekly bolus dose is missing, the average weekly (or daily) total insulin dose and the basal/total insulin dose ratio will be set as missing for the analysis.

The insulin dose analysis will be conducted for

- both daily dose and weekly dose in units for each of the basal, bolus, and total insulin, respectively.
- dose in U/kg/day for basal, bolus, and total insulin, respectively, and
- basal/total insulin dose ratio.

4.4.2.1.3. Analysis of Fasting Blood Glucose

The analysis of fasting blood glucose (FBG), measured by SMBG, will be analyzed (in both CN and SI units). If a subject does not indicate which BG measurement was fasting, the FBG value will be assigned programmatically by designating the FBG as the first measurement between 5am-10am. These programmatically derived FBG values will also be included in the analysis.

4.4.2.2. Other Safety Endpoints

The safety measures based on CGM data will be analyzed as described in Section 4.4.2.1.1. 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. Diabetes Treatment Satisfaction Questionnaire

Diabetes Treatment Satisfaction Questionnaire-Status

The Diabetes Treatment Satisfaction Questionnaire-Status Version (DTSQs) (Bradley and Lewis 1990; Bradley 1994) is a diabetes-specific patient-reported outcome instrument that assesses the overall treatment satisfaction and perceived frequency of hyperglycemia and hypoglycemia. It is appropriate for use in both T1D and Type 2 diabetes mellitus. The DTSQs consists of 8 items that assess treatment satisfaction as well as concerns about hyperglycemia and hypoglycemia over the previous few weeks prior to the visit. Each item is rated on a 7-point Likert scale. Items 1 and 4 through 8 are rated from 0 (very dissatisfied) to 6 (very satisfied) and can be summed up to produce a treatment satisfaction score ranging from 0 to 36. Items 2 and 3 are scored individually, evaluate the perceived frequency of hyperglycemia and hypoglycemia, and are rated from 0 (none of the time) to 6 (most of the time).

The collection of the DTSQs is planned prior to the initiation of study treatment. The total scores of Items 1 and 4 through 8 and the individual scores of Items 2 and 3 will be summarized. A Wilcoxon rank-sum test will be used for treatment comparison.

Diabetes Treatment Satisfaction Questionnaire-Change

The Diabetes Treatment Satisfaction Questionnaire-Change Version (DTSQc) (Bradley 1999) was designed to overcome potential ceiling effects in the status version. The DTSQc has the same 8 items as the status version but is reworded slightly to measure the change in treatment satisfaction rather than absolute treatment satisfaction. Each item is scored on a scale of -3 to +3. For all items except Item 2 (perceived frequency of hyperglycemia) and Item 3 (perceived frequency of hypoglycemia), the higher the score, the greater the improvement in treatment satisfaction. A score of 0 represents no change. For Items 2 and 3, the lower the score, the better

the perception. The ratings for Items 1 and 4 through 8 are summed to obtain a total treatment satisfaction score ranging from -18 to 18. Items 2 and 3 are scored individually.

The collection of the DTSQc is planed after the initiation of study treatment. The total scores of Items 1 and 4 through 8 and the individual scores of Items 2 and 3 will be summarized. A Wilcoxon rank-sum test will be used for treatment comparison.

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

Per copyright owner, the QualityMetric Health Outcomes™ Scoring (PRO_CoRe Version 2.0) 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.

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 SD 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). The last non-missing postbaseline observations will be analyzed by an ANCOVA model using the independent variables of treatment, strata (country, baseline HbA1c stratum [<8.0%, ≥8.0%], CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), and baseline value of the dependent variable as independent variables.

4.4.2.3.3. EQ-5D-5L

The European Quality of Life Questionnaire (EQ-5D-5L) (EuroQol 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 <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 the 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). The last non-missing postbaseline observations will be analyzed by an ANCOVA model using the independent variables of treatment, strata (country, baseline HbA1c stratum [<8.0%, ≥8.0], CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), and baseline value of the dependent variable as independent variables.

4.4.2.3.4. 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 using a Wilcoxon rank-sum test for treatment comparison.

Preference

This is a Lilly-developed, participant-completed question to understand the participant's preference for their prestudy or current study treatment. The question is rated on a 5-point scale with responses ranging from "strongly prefer the study insulin" to "strongly prefer my previous insulin." The question also includes a "not applicable" option for participants that stayed on the same insulin in the treatment phase.

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

4.5. Tertiary Endpoint Analysis

4.5.1. Tertiary Efficacy Endpoints

For continuous endpoints, either an ANCOVA model using data from EAS1 or MMRM model using data from EAS2 will be performed as described in Section 4.4.2.1.

For analysis of the binary outcomes, the details are provided in the table below:

Analysis Population	All participants in EAS1 with non-missing baseline measure
Analysis Data	All non-missing observations at baseline and at time point of interest regardless of the use of study intervention or rescue medications.

Endpoint	• Binary outcome of HbA1c <7% or ≤6.5% at time point of interest with 'Yes' indicating achieving HbA1c target.
	• The composite of
	  ○ binary outcome of HbA1c <7% at Week 26, and,
	  ○ binary outcome of no nocturnal level 2 hypoglycemia during treatment phase up to Week 26.
	• The composite of
	  ○ binary outcome of HbA1c <7% at Week 26, and,
	  ○ binary outcome of no level 3 severe hypoglycemia during treatment period up to Week 26
	with "Yes" indicating achieving the target (in respective endpoints defined above).

Missing Data	• For HbA1c, missing values at the specified timepoints will be imputed using the same method for the primary endpoint (Section 4.3.2). • For hypoglycemia that are included in the composite endpoints, a participant who discontinued the treatment period before Week 26 (Visit 22) is considered as a non-responder (that is, experienced the event).
Analysis Model	These endpoints will be analyzed using a logistic regression model including independent variables of treatment, strata (country, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), and baseline HbA1c value (and, *for the composite endpoint,* baseline incidence of hypoglycemia and interaction between baseline HbA1c value and baseline incidence of hypoglycemia. If the model fails to converge, the interaction term will be removed). The unconditional treatment group effect will be assessed based on a robust variance estimator for g-computation estimators (Ye et al. 2023). The estimated treatment group-specific odds ratio, p-value, and 95% CI will be used for treatment comparison. The statistical inference will be based on the multiple imputation framework by Rubin (1987).

Abbreviations: EAS1 = Efficacy Analysis Set 1; HbA1c = hemoglobin A1c.
Note: Levels of hypoglycemia events and nocturnal events are defined in Section 4.6.3.1.1.

4.5.2. 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, AEs, vital signs, weight, hypoglycemia, laboratory measures, and immunogenicity. All safety analyses will be based on the Safety Analysis Set

(SS). Unless otherwise specified, the safety analysis period will include both the treatment period and follow-up period.

Percentages will be calculated using the SS 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 noted, Fisher's exact test will be used for the treatment comparison and risk difference and 95% confidence intervals will be provided. Additionally, an odds ratio and 95% confidence intervals will be provided for selected tables in addition to the risk difference.

For continuous safety variables (for example, laboratory measures, vital signs, and weight), descriptive statistics for the observed and change from baseline at scheduled visits during the treatment and the follow-up period will be provided. For selected laboratory measures (that is, 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 effects; baseline of the dependent variable as a covariate; and compound symmetry as the variance-covariance structure. The last postbaseline observation in the study will be analyzed by the ANCOVA model with the independent variables of treatment and baseline of the dependent variable.

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.

The treatment-emergent analyses will use all data in the analysis period, including scheduled and unscheduled measurements. The safety analysis period for treatment-emergent analyses starts after the first dose and ends at the last visit in the study, including the safety follow-up period.

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

Exposure on study treatment will be calculated as follows:

- LY3209590: date of the last treatment administration - date of first treatment administration + 7 days.
- Insulin degludec: date of the last treatment administration - date of first treatment administration + 1 day.

Total participant-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 are reported to worsen in severity from baseline will be considered treatment-emergent AEs (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 analyses related to AEs.

Analysis	Details
Overview of AEs	• number and percentage of participants who experienced • SAEs • deaths • discontinuation from the study treatment due to an AE • discontinuation from the study due to an AE • TEAEs, and • TEAEs related to study treatment.
Summary by PT within SOC	• TEAEs • Maximum Severity TEAEs • SAEs, 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.
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. Events will be ordered by decreasing risk difference and by decreasing frequency in LY3209590 group, respectively. • 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 events will be provided: • SAEs 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.

Abbreviations: AE = adverse event; LLT = lowest level term; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SMQ = Standardised MedDRA query; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

4.6.2.1. Safety Topics of Special 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 Preferred Term (PT) will be provided. The incidence and event rate during the treatment period will be analyzed using the method described in Section 4.6.3.1.1. 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:

- a prespecified criteria to derive events from the e-diary database (see definition in Appendix 10 [Section 6.10]), and
- investigator assessment and clinical judgment to determine if the participant experienced repeated hypoglycemia.

Identification of P-R hypoglycemia based on investigator reporting is precipitated by a hypoglycemic event a participant reported having a potential clinical treatment or outcome. This information will trigger an e-mail alert notifying the investigator to evaluate the event. Hypoglycemic events that trigger alerts to investigators are those in which participants report in the e-diary having required treatment with glucagon or intravenous glucose, resulted in coma, motor vehicle accident or other trauma, hospitalization, or emergency medical care.

Upon receiving the e-mail notification, the 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?"* The investigator should select *"Yes"* or *"No"* as an answer.

P-R hypoglycemia events and participants who experience P-R hypoglycemia will be identified by one or both of the 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 a 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 reported with 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 nested within each SMQ in decreasing order of risk difference.

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 (ISRs) 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 ISR follow-up form completed by the investigator for each incidence of an ISR considered by the investigator to be related to study basal insulin. A summary of the number of participants with reported events meeting any of the following categories will be provided:

- MedDRA High Level Term (HLT) of Injection site reactions
- MedDRA HLT of Administration site reactions NEC, and
- 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 reporting at least 1 AE meeting any of the above categories
- the number of participants reporting any AE in each category, and
- the number of participants reporting any AE for each PT within a specific category.

The PTs will be listed for summary within each category in decreasing order of 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 SMQs:

- *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

Diabetic ketoacidosis (DKA) will be searched by MedDRA PTs from all TEAEs. The number and percentage of participants experiencing treatment-emergent DKA will be summarized by PT and treatment. The following PTs will be used in search of DKA:

- *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

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

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 the *Hypokalaemia* SMQ (20000233). A summary of the number of participants with treatment-emergent events meeting the SMQ narrow search criteria by PT will be provided.

4.6.2.1.10. Hyperglycemia

Study treatments were designed as treatments for hyperglycemia in patients with diabetes. Therefore, hyperglycemia is usually not reported as an AE in diabetes studies. However, if a participant develops severe, persistent hyperglycemia after randomization, 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

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 Events Committee will adjudicate the events in a consistent and unbiased manner. Events include

- death
- cardiac ischemic events (including myocardial infarction or *hospitalization for unstable angina*)
- cerebrovascular events (including stroke or transient ischemic attack)
- hospitalization for unstable angina
- hospitalization for heart failure, and
- coronary revascularization procedure.

Only major adverse cardiovascular events (MACE) confirmed by the adjudication committee will be considered as AEs of special interest. A listing of MACE reported by the investigator, including the reported term and adjudication results, will be provided.

4.6.2.1.12. Medication Errors 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 deviation (IPD) indicative of multiple doses, according to the Trial Issue Management Plan. These events are considered IPDs because of their potential to impact participants' safety. For this same reason, these events are considered of special interest among all medication error AEs reported in the trial's CRF.

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 the 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. The 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

Hypoglycemia events will be derived in the analysis datasets and documented as Level 1, Level 2, and Level 3 (severe hypoglycemia), according to definitions based on the American Diabetes Association criteria:

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

The Level 2 and Level 3 events are considered as 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.

The 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 one 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 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 events confirmed by investigators based on clinical judgment and through events identified by a prespecified criteria (see Section 4.6.2.1.2 and Appendix 9 [Section 6.9] for details) using information based on participant-reported hypoglycemia.

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

Endpoint	Analysis Period[a]	Statistical Method
Event rate of Level 1 hypoglycemia events (events/participant/year) • all documented	Baseline, Weeks 0-6, 0-12, 0-26, 0-52, 12-26, 26-52, and the posttreatment period	Negative binomial regression with treatment, baseline HbA1c, and baseline Level 1 hypoglycemia rate as covariates and log (exposure/365.25 days) as the offset in the model
Event rate of Level 2 hypoglycemia events (events/participant/year) • all documented	Baseline, Weeks 0-6, 0-12, 0-26, 0-52, 12-26, 26-52, and the posttreatment period	Negative binomial regression with treatment, baseline HbA1c, and baseline Level 2 hypoglycemia rate as covariates and log (exposure/365.25 days) as the offset in the model
Event rate of Level 3 hypoglycemia events (events/participant/100 years) • all documented	Baseline, Weeks 0-26, 0-52, 26-52, and the posttreatment period	Negative binomial regression with treatment and baseline HbA1c, and baseline Level 3 hypoglycemia rate as covariates and log (exposure/36525 days) as the offset in the model If the number of events is too small to run the negative binomial regression, the 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 10 [Section 6.10] for details) will be used for treatment comparison.
Event rate of Level 2/3 hypoglycemia events (events/participant/year) • all documented • nocturnal, and • non-nocturnal	Baseline, Weeks 0-6, 0-12, 0-26, 0-52, 12-26, 26-52, and the posttreatment period	A negative binomial regression with treatment, baseline HbA1c, and baseline hypoglycemia rate of the same hypoglycemia type as covariates and log (exposure/365.25 days) as the offset in the model. 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[b].
Incidence of Level 1 hypoglycemia events • all documented	Baseline, Weeks 0-6, 0-12, 0-26, 0-52, 12-26, 26-52, and the posttreatment period	Logistic regression with treatment, baseline HbA1c, and baseline Level 1 hypoglycemia incidence as covariates
Incidence of Level 2 hypoglycemia events • all documented	Baseline, Weeks 0-6, 0-12, 0-26, 0-52, 12-26, 26-52, and the posttreatment period	Logistic regression with treatment, baseline HbA1c, and baseline Level 2 hypoglycemia incidence as covariates
Incidence of Level 3 hypoglycemia events • all documented	Baseline, Weeks 0-26, 0-52, 26-52, and the posttreatment period	Logistic regression with treatment and baseline HbA1c as covariates

Endpoint	Analysis Period[a]	Statistical Method
Incidence of Level 2/3 hypoglycemia events • all documented • nocturnal, and • non-nocturnal	Baseline, Weeks 0-6, 0-12, 0-26, 0-52, 12-26, 26-52, and the posttreatment period	Logistic regression with treatment, baseline HbA1c, and baseline hypoglycemia incidence of the same hypoglycemia type as covariates.
Potential persistent-recurrent hypoglycemia events • identified by investigators and • identified by a prespecified criteria (defined in Appendix 9 [Section 6.9])	Safety analysis period (see the definition in Section 4.6)	The number of participants with at least 1 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; mITT = modified intent-to-treat.

[a] For analysis for baseline period, negative binomial regression or logistic regression will not include baseline HbA1c and baseline hypoglycemia for treatment companions.

[b] (Nelson 2003)

Note: The yearly hypoglycemia rate during the defined period is calculated by the number of hypoglycemic events within the period/number of days a participant is at risk within the period × 365.25. For rare events, 100-year rate will be provided. The hypoglycemia incidence during the defined period indicates if the participant has at least 1 hypoglycemia event within the period (yes/no).

4.6.3.1.1.1. **Sensitivity Analysis**Error! No document variable supplied.

A sensitivity analysis will be done for selected hypoglycemic endpoints where all hypoglycemic events are considered 1 hypoglycemic episode 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 Period	Statistical Method
Event rate of Level 1 or Level 2 hypoglycemic events (events/participant/year): • 24-hour	Baseline, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment period	Negative binomial regression with treatment, baseline HbA1c and baseline Level 1 or Level 2 hypoglycemia rate as covariates, log (exposure/365.25 days) as the offset in the model.
Event rate of Level 2 hypoglycemic events (events/participant/year): • 24-hour	Baseline, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment period	Negative binomial regression with treatment, baseline HbA1c and baseline Level 2 hypoglycemia rate as covariates, log (exposure/365.25 days) as the offset in the model.

Endpoint	CGM Period	Statistical Method
Event rate of Level 2 hypoglycemic events ending with ≥70 mg/dL (events/participant/year): • 24-hour	Baseline, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment period.	Negative binomial regression with treatment, baseline HbA1c and baseline rate for Level 2 hypoglycemia ending with ≥70 mg/dL as covariates, log (exposure/365.25 days) as the offset in the model.
Incidence of Level 1 or Level 2 hypoglycemic events: • 24-hour	Baseline, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment period.	Logistic regression with treatment, baseline HbA1c and baseline Level 1 or Level 2 hypoglycemia incidence 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 period.
Incidence of Level 2 hypoglycemic events: • 24-hour	Baseline, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment period.	Logistic regression with treatment, baseline HbA1c and baseline Level 2 hypoglycemia incidence as covariates.
Incidence of Level 2 hypoglycemic events ending with ≥70 mg/dL: • 24-hour	Baseline, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment period.	Logistic regression with treatment, baseline HbA1c and baseline incidence for Level 2 hypoglycemia ending with ≥70 mg/dL as covariates.
Duration of Level 1 or Level 2 hypoglycemic events: • 24-hour	4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52.	MMRM model will include treatment, strata (country, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no], baseline HbA1c stratum), time and treatment-by-time interaction as fixed effects, and baseline duration as a covariate.
	0-26 and 0-52.	For each timepoint, ANCOVA model with treatment, strata (country, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no], baseline HbA1c stratum) as fixed effects, and baseline duration as a covariate.
	Baseline and post-treatment period	ANOVA models only include treatment.

Endpoint	CGM Period	Statistical Method
Duration of Level 2 hypoglycemic events: • 24-hour	Baseline, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment 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, 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52, 6 weeks prior to Weeks 22 and 32, 0-12, 12-26, 26-52, 0-26, 0-52, posttreatment period.	Same models as for Level 1 or Level 2 hypoglycemic events.

Abbreviations: ANOVA = analysis of variance; ANCOVA = analysis of covariance; CGM = Continuous Glucose monitor; HbA1c = hemoglobin A1c; MMRM = mixed model for repeated measures.

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

4.6.3.2. Laboratory and Adverse Event for Hepatic Safety

Hepatic laboratory values 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.

Table BDCY.4.1 lists summary tables, figures, and listings (TFLs) for the analysis of hepatic laboratory data.

Table BDCY.4.1. Summary Tables, Figures, and Listings Related to Hepatic Safety

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 (1X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) 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 (1X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) 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 (2X) and 3 times (3X) 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 (2X), 5 times (5X), and 8 times (8X) 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 (2X) and 5 times (5X) 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 (2X) 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) • Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015) 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.

Analysis	Details
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 2X ULN and 3X ULN, respectively. A potential Hy's law case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2X ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3X ULN, without cholestasis (defined as ALP less than 2X 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 2X ULN and 3X ULN, respectively. A potential cholestatic liver injury case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2X ULN within 30 days after maximum postbaseline ALP equal to or exceeding 3X 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
- lipid measures: triglycerides, total cholesterol, low-density lipoprotein (LDL)-C, and high-density lipoprotein (HDL)-C (results from fasting samples)

The 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 participants with elevated or low values meeting specified levels (see Appendix 10 [Section 6.10]) at any post-baseline (including scheduled and unscheduled measurements) will be summarized and compared between treatment groups using risk difference, odds ratio and 95% confidence interval.

A listing of abnormal laboratory analytes collected quantitatively (high or low during postbaseline using Level 2 definitions in Appendix 10) and qualitatively (abnormal during postbaseline) will be provided, including participant identification, treatment group, laboratory sample collection day (that is, days from the start of study drug), analyte name, abnormal result, and reference low or high limits (Level 2 cut-off value).

Scatter plots of maximum baseline-by-maximum postbaseline measurements and minimum baseline-by-minimum postbaseline 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. Analysis data 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 blood pressure (BP), diastolic BP, pulse, weight, and body mass index (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[a].

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[b].
	  ○ Systolic BP (mm Hg):
	  ▪ Low: Level 1: <90
	  ▪ Level 1: ≥90, Level 2: ≥120, Level 3: ≥140, Level 4: ≥160, Level 5: ≥180
	  ○ Diastolic BP (mm Hg):
	  ▪ Low: Level 1: <60
	  ▪ 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 CTC 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; MMRM = mixed model for repeated measures.

[a] See also: Table 6.2 from the Analyses and Displays for Labs white paper (PHUSE 2022).

[b] (FDA 2022).

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**Error! No document variable supplied.

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 treatment-emergent antidrug antibodies (TE ADA) if the participant has a non-missing baseline ADA result, and at least 1 non-missing 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 a 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 the 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.

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 Analysis for HbA1c

The subgroups for analyzing HbA1c and change in HbA1c from baseline to Week 26 will be defined as (a subgroup category will not be included if there are less than 10 participants in the category)

- baseline HbA1c stratum (<8.0% and ≥8.0%)
- region (US and non-US)
- region (North America, South America, Europe, Asia)
- age as (<40 years and ≥40 years)
- age as (<65 years and ≥65 years)
- CGM use prior to study entry (yes and no)
- carbohydrate counting for prandial insulin dosing (yes and no)
- gender (female and male)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- race (White, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Black or African American)
- estimated Glomerular Filtration Rate (eGFR) at baseline (<60, ≥60 to <90 and ≥90 mL/min/1.73 m^2), and
- duration of diabetes (<median and ≥median).

For treatment regimen estimand: Analyses for HbA1c and its change will be performed using the same ANCOVA model with the same independent variables as described in Section 4.3.2, separately for each subgroup. The missing values will be imputed by multiple imputation method same as the primary analysis for treatment regimen estimand. 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]).

For efficacy estimand: Analyses for HbA1c and its change will be performed within each subgroup using the same MMRM model for the efficacy estimand described for the primary analysis in Section 4.3.2. In addition, the interaction effects be assessed using the model will include 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.

4.7.2.2. Subgroup Analysis for Participant-Reported Hypoglycemic Events

The subgroups, for analyzing documented Level 2/3 hypoglycemia and non-nocturnal and nocturnal hypoglycemia rates during 0 to 52 weeks, will be defined as

- baseline HbA1c stratum (<8.0% and ≥8.0%)
- region (US and non-US)

- region (North America, South America, Europe, Asia)
- age as (<40 years and ≥40 years)
- age as (<65 years and ≥65 years)
- CGM use prior to study entry (yes and no)
- carbohydrate counting for prandial insulin dosing (yes and no), and
- eGFR at baseline (<60, ≥60 to <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 4.6.3.1.1), separately for each subgroup. The interaction effects will be evaluated using a full model using a negative binomial regression including the same independent variables plus factors of subgroup, 2-way interaction of subgroup, and treatment.

4.8. Interim Analyses

4.8.1. Data Monitoring Committee (DMC)

An independent, external Data Monitoring Committee (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. The study team will remain blinded to study treatment until the planned unblinding occurs. The DMC will be conducted to maintain study integrity. Details of the DMC are 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 670 participants will be randomized to LY3209590 and insulin degludec in a 1:1 ratio. With the assumption of 15% dropout at Week 26, approximately 284 and 284 participants will complete 26 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 Visit 22 (Week 26) in HbA1c in participants with T1D currently basal-bolus insulin.

Assuming an NIM of 0.4%, no true difference between treatment groups, and an SD of 1.1%, 568 completers (284 on LY3209590 and 284 on insulin degludec) will provide at least 99% statistical power to show noninferiority between LY3209590 and insulin degludec using the upper limit of a 2-sided 95% CI (LY3209590 - insulin degludec). This sample size also has at least 90% statistical power to show noninferiority between LY3209590 and insulin degludec using a 0.3% NIM at Week 26.

The 568 completers will provide 90% statistical power to demonstrate the superiority (LY3209590 vs insulin degludec) of change in HbA1c from baseline to 26 weeks (assuming an SD of 1.1% and true mean difference of -0.3%) using the α of 0.05.

The 568 completers will provide at least 99% statistical power to show the superiority of the percentage of time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, measured by CGM 4 weeks prior to Week 26 between LY3209590 and insulin degludec (assuming an SD of 10% and true mean difference of 5%) using the α of 0.05.

The 568 completers will provide 80% statistical power to show the superiority of the event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during the treatment phase up to Week 52 (assuming event rates of 3.37 [SD = 7.13] and 4.87 [SD = 7.13] events per participant per year for LY3209590 and insulin degludec, respectively) using a negative binomial distribution α 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 (<40 years and ≥40 years, <65 and ≥65, <75 and ≥75, <85 and ≥85 years), sex, ethnicity, race, country, region, height, weight (kg), body mass index (BMI: kg/m^2), BMI groups (<25, ≥25 and <30, ≥30 and <35, ≥35 kg/m^2), eGFR groups (≥30 and <60, ≥60 and <90, ≥90 mL/min/1.73 m^2), 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), type of pre-study basal insulin, type of pre-study prandial insulin, carbohydrate counting for prandial insulin dosing (Yes and No), and CGM use prior to study entry (Yes and No) 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 informed consent and preexisting conditions are conditions that are still ongoing at informed 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 algorithm for both study treatments. The investigator will calculate the algorithm-recommended dose based on the participant's fasting BG and hypoglycemia occurrence reported in e-diary. CGM data, including 24-hour glucose profiles and additional self-monitored BG monitoring (if applicable), should also be considered. If the investigator does not agree with the algorithm-recommended dose, the investigator will prescribe another dose for the participant and provide the reason of not following the algorithm-recommended dose and choose a reason for not following the algorithm recommended dose from a prespecified list of terms. 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.

Study personnel or the participant will administer the first study dose of LY3209590 at the site. Insulin degludec can be taken at the site or after the visit, depending upon whether the study visit

timing coincides with the participant's usual time to administer basal insulin. 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 AEs, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Nonserious 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
    - 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
    - the total number of deaths causally related to treatment.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participant 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 clinical study report, 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 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, with either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment.

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

6.5. Appendix 5: Protocol Deviations

Important protocol deviations (IPDs) are the deviations from the study protocol that may compromise the data integrity and participants' 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

For all study participants meeting study entry criteria, a CGM device will be inserted and activated at (Visit 2). Participants will be unblinded to the CGM system and wear the study-provided CGM during the study duration.

For the primary analysis, the CGM data will be included in the analysis only if at least 70% of the total measures in the analysis period are obtained (defined as a valid CGM period). For example, the 24-hour period will have 288 measures and the minimum number of measures will be 202. All the CGM derivations are based on the data from valid CGM period unless otherwise specified. A sensitivity analysis will be done for selected parameters by including CGM days with at least 10% of data and at least 3 such CGM days within the given CGM period.

The CGM variables will be derived for each CGM day when the analysis data meet the above requirement. The CGM variables for an analysis visit/period will be derived for participants with at least 3 valid CGM days during the corresponding analysis visit/period. For the analysis visits, the CGM readings from approximately 2 weeks prior to Week 0 (Visit 3), 4 weeks prior to Weeks 4, 8, 12, 16, 26, 36, 40, 44, 48, and 52 (Visit 7, 11, 15, 17, 22, 25, 26, 27, 28, and 29), 6 weeks prior to Weeks 22 and 32 (Visit 20 and 24) and 4 weeks prior to the end of safety follow-up (Visit 802) will be used. To understand the overall control in different periods (for example, the titration period), the CGM variables may also be derived for the following analysis periods: 0 through 12, 12 through 26, 26 through 52, 0 through 26, and 0 through 52 weeks of treatment period.

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,
- 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.

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

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

Period	Definition	Minimum Valid CGM Time Period for a Session
Valid CGM day (0000-2359)	≥70% of expected values available (≥202 of 288 values)	≥3 valid CGM days within a visit defines a valid CGM visit. A valid CGM period only includes valid CGM visits.
Valid CGM nighttime (0000-0559)	≥70% of expected values available (≥50 of 72 values)	≥3 valid CGM nighttime within a visit defines a valid CGM visit. A valid CGM period for nighttime only includes valid CGM visits.
Valid CGM daytime (0600-2359)	≥70% of expected values available 151 of 216 values)	≥3 valid CGM daytime within a visit defines a valid CGM visit. A valid CGM period for daytime only includes valid CGM visits.

For the primary analysis, CGM data must meet above criteria for the period in order to be included as a valid CGM period. Additionally, sensitivity analysis will be performed for selected parameters by including all available CGM data.

The ambulatory glucose profile during the 24-hour period will be generated with interquartile ranges, at treatment group-level by visit/period, 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 for each analysis visit/period defined in Section 6.6 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 analysis visit/period 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%
- 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)
- >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 4 or 6 weeks prior to the given

analysis visit as defined in Section 6.6 for 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) in 4 or 6 weeks prior to the given analysis visit defined in Section 6.6 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:

Hypoglycemia Level	Stating Time	Ending Time	Duration
Level 1 or 2 hypoglycemia (BG <70 mg/dL [3.9 mmol/L])	Time of the 1st BG of BGs <70 mg/dL for ≥15 consecutive minutes	Time of the last BG of the BGs ≥70 mg/dL for ≥15 consecutive minutes	Time of the last BG <70 mg/dL – time of the 1st BG <70 mg/dL
Level 2 hypoglycemia (BG <54 mg/dL [3.0 mmol/L])	Time of the 1st BG of BGs <54 mg/dL for ≥15 consecutive minutes	Time of the last BG of the BGs ≥54 mg/dL for ≥15 consecutive minutes	Time of the last BG <54 mg/dL – time of the 1st BG <54 mg/dL
Level 2 hypoglycemia ending with BG ≥70 mg/dL (start with BG <54 g/dL [3.0 mmol/L], end with BG ≥70 mg/dL [3.9 mmol/L])	Time of the 1st BG of BGs <54 mg/dL for ≥15 consecutive minutes	Time of the last BG that ensures the BGs ≥70 mg/dL for 15 consecutive minutes	Time of the last BG <70 mg/dL – time of the 1st BG <54 mg/dL

Abbreviation: BG = blood glucose; CGM = continuous glucose monitor.
Note: Starting time and ending time are regardless of number of BG readings.
BG was captured using a CGM.

If the truncated time interval is >7 minutes but ≤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 makes 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.

If an episode started and continued until the end of a CGM period, then the episode ends at the end of CGM period.

The average duration, incidence, event rate of the Level 1 or 2 and Level 2 hypoglycemia episodes will be analyzed for each CGM period as planned in Section 4.6.3.1.2. The average duration will be calculated by dividing the sum of the duration of individual episodes within 4 weeks prior to the given visit by the number of episodes and used in the analysis.

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

The duration (minute) 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 averages of the analysis visit will be used as the mean glucose of the given analysis visit and 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

$BG_{k,i}$ 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 4 weeks prior to the given visit.

Within-day glucose SD (Rodbard 2009):

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

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

$$CV = \frac{1}{m}\sum_{k=1}^{m} CV_k = \frac{1}{m}\sum_{k=1}^{m} \frac{SD_k}{(\frac{\sum_{i=1}^{n} BG_{k,i}}{n})} \times 100$$

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 averaged across days within 4 weeks prior to the given visit. 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 4 weeks prior to the given visit 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.

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

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*, and
- *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*, and
- *Visceral oedema*.

6.9. Appendix 9: Definition for Persistent-Recurrent Hypoglycemia by Programming

A P-R hypoglycemia based on a 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 (<54 mg/dL [3.0 mmol/L]) and is followed by more episodes of hypoglycemia (<70 mg/dL [3.9 mmol/L]), within the day of the initial episode

AND

b) is followed by at least 1 episode of hypoglycemia (<70 mg/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 of a P-R hypoglycemia event is illustrated in Figure BDCV.6.1.

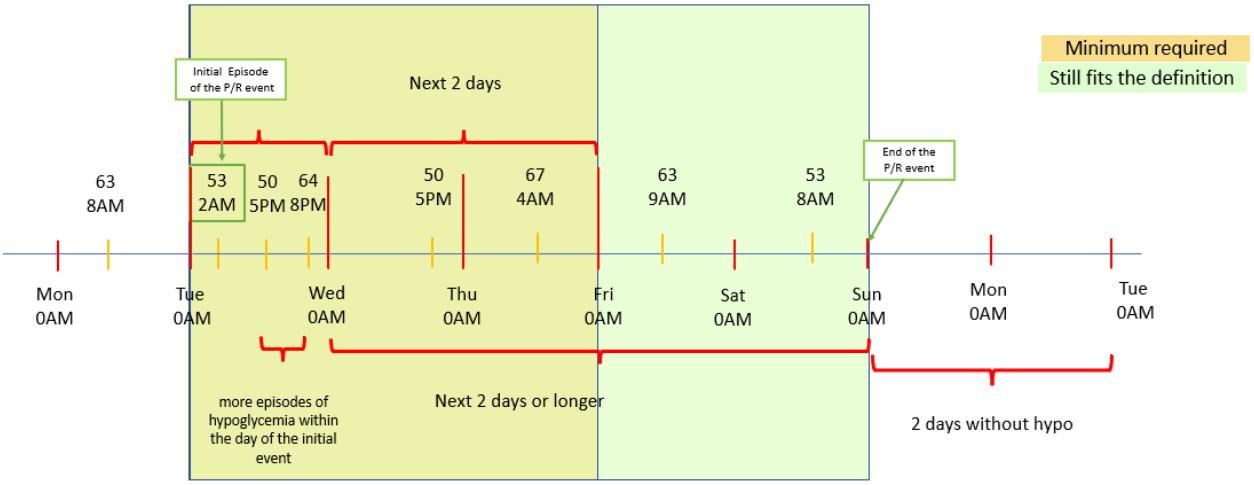

Figure BDCV.6.1. Illustration of persistent-recurrent hypoglycemia by programming.

6.10. Appendix 10: 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 x baseline	≥2.0 x baseline	≥3.0 x baseline
eGFR, decrease (ml/min/1.73m2)	≥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	>10000	>20000
Neutrophils, low (cells/µL)	<2000	<1000	<500
Eosinophils, high (cells/µL)	>650	>1500	>5000
Coagulation Studies			
Prothrombin time, increase (sec)	>1.1 x ULN	>1.3 x ULN	>1.5 x ULN

Abbreviations: eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; ULN = upper limit of normal.

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

6.11. Appendix 11: Empirical Estimation of Relative Event Rate

Traditionally, the 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 T1D participants, 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 1 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 participant *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

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

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

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

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 k groups (k ≥ 2),

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

A chi-square test (with degrees of freedom = 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 Japan

Separate analyses will be performed for participants participating in Study BDCY from the Japan-based Japanese population.

The analysis methods will be similar to those described for the main part of this SAP. Efficacy analyses for Japan will be based on the efficacy estimand.

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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