Statistical Analysis Plan I8H-MC-BDCU Version 4

A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Trial to Evaluate the Efficacy and Safety of LY3209590 Compared With Insulin Degludec in Participants With Type 2 Diabetes Currently Treated With Basal Insulin (QWINT-3)

NCT05275400

Approval Date: 27-May-2024

Title Page

Protocol Title: A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Trial to Evaluate the Efficacy and Safety of LY3209590 Compared with Insulin Degludec in Participants with Type 2 Diabetes Currently Treated with Basal Insulin (QWINT-3)

Protocol Number: I8H-MC-BDCU(b)

Compound Number: LY3209590

Short Title: Efficacy and Safety of the Once-Weekly Basal Insulin LY3209590 Therapy Compared with Daily Insulin Degludec in Adults with Type 2 Diabetes Treated with Basal Insulin

Acronym: QWINT-3 (Once-Weekly Insulin Therapy)

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 129390

EudraCT: 2021-002569-16

Document ID: VV-CLIN-122290

Table of Contents

Version history

The Statistical Analysis Plan (SAP) Version 1 was approved on 03 March 2022, prior to the first participant visit of the study. The SAP Version 1 was based on the Protocol I8H-MC-BDCU and the amendment Protocol I8H-MC-BDCU(a) which were approved on 08 November 2021 and 28 January 2022, respectively.

The SAP Version 2 was approved on 17 May 2022, prior to the first production transfer of blinded data. The SAP Version 2 was based on the amendment Protocol I8H-MC-BDCU(b) and the I8H-MC-BDCU protocol addendum (2.1), approved on 13 May 2022 and 22 February 2022 respectively, in addition to the above protocol and protocol amendments.

The SAP Version 3 was approved on 20 Jan 2024, prior to the final production data. The SAP Version 3 was based on the questions from different regulatory agencies and required updates, in addition to the above protocol and protocol amendments.

This SAP is the fourth version based on the recommendations from the United States Food and Drug Administration (FDA), in addition to the above protocol and protocol amendments. This SAP is approved prior to the database lock.

Table 1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	Prior to the first participant visit. 03 March 2022	Not Applicable	Original version
2	Prior to the first production transfer of blinded data. 17 May 2022	Section 1.1: Added PK/PD Endpoint in Tertiary	Integrated from BDCU(a)
		Section 3: Updated the analysis populations.	To meet the anticipated requirement for excluding inadvertently enrolled participants in some countries.
		Section 4.3.3: Changed the Sensitivity Analysis: A 2-way tipping point analysis has been added. Imputation under the noninferiority null hypothesis has been elaborated.	For clarification and to address regulatory feedback.
		Section 4.4.2.3: For SIM-Q and both the Basal Insulin Experience questionnaires, treatment comparison methodology has been changed to Wilcoxon rank sum test.	Wilcoxon rank sum test is more appropriate than Chi-Square test for ordinal data.
		Section 4.5.1: For Tertiary Efficacy Endpoints: Updated the analysis for the longitudinal binary variables of achieving HbA1c targets.	To handle the missing data.

SAP Version	Approval Date	Change	Rationale
		Updated the analysis for the longitudinal binary variables of achieving HbA1c targets without nocturnal hypoglycemia.	
		Section 4.6.3.1: Replaced 365.25 with 36525 for level 3 hypoglycemia event rate analysis.	Correction.
		Section 4.7.2: New subgroups are added to the analysis.	For clarification and to address regulatory feedback.
		Section 6.6 (Appendix 6): Added text "for participants with at least 3 valid CGM days."	To define a valid CGM session.
		Section 6.6.1: Added definition of average daily time in hypoglycemia relative to dose administration.	Added a CGM variable for exploration.
		Added Section 6.10 (Appendix 10)	Per regulatory input for definition of Persistent/ Recurrent Hypoglycemia
		Added Section 6.11 (Appendix 11)	Per PMDA request.
		Throughout SAP: Minor editorial changes.	For clarity.
		Throughout SAP: Following glucose values in mg/dL, added corresponding values in mmol/L.	Due to different regulatory requirements.
		Throughout SAP: "Visit xx (Week xx)" references are changed to "Week xx (Visit xx)."	To be consistent with the objectives.
3	prior to the database lock 20 Jan 2024	Added, in Section 2.1, the plan for multiplicity adjustment for primary and key secondary efficacy objectives – the details of type I error control strategy.	To finalize 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 define Baseline and postbaseline observations and related analysis.	Correction.
		Added, in Section 4.2, analysis of time-to-event of interest in disposition.	Amended as per 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 accommodate Regulatory requirements

SAP Version	Approval Date	Change	Rationale
		Added subsections to Section 4.4.2.	For clarification of each supportive secondary endpoints.
		Moved tertiary patient reported outcomes to Section 4.5.3 from Section 4.4.2.3.	Correction.
		Added subsections in 4.5.1 to explicitly mention analysis method for tertiary outcome measures. Methodology for multiple imputations for missing data have been updated.	For clarification.
		Changes were made throughout Section 4.6.2 to align with the PSAP. Added analysis for P-R hypoglycemia and medication error of interest in Section 4.6.2.1 safety topic of interest.	For alignment with PSAP.
		Made subsections to Section 4.6.3.1 (hypoglycemic events) to accommodate analysis from patient reported hypoglycemia and newly added CGM based derived hypoglycemia. Added rule to identify as single hypoglycemia event from the patient reported hypoglycemia events that occurred within 60 minutes to each another. Changed analysis of event rates to accommodate baseline rate instead of baseline incidences in the models.	For clarification.
		Changes were made throughout Sections 4.6.3.2, 4.6.3.3 and 4.6.3.4 and added Section 6.12 to align with the PSAP.	For alignment with PSAP.
		Edited Section 4.7.1 and Section 4.7.2 for clarification and reorganizing of the corresponding analyses. Hence, added Section 6.13 to clarify the interaction effect for subgroup analysis.	For clarification.
		Edited and added texts in Section 6.6 to clarify handling of missing CGM data and definitions of CGM derived hypoglycemic episodes.	For clarification.
		Throughout the SAP made minor changes and reorganization	For clarity, no change to analysis methodologies, so not detailed
4	prior to the database lock	Added sensitivity analysis for primary (in Section 4.4.3) and key secondary analyses (in Section 4.4.1.3) of continuous endpoints to	To comply with FDA's advice.

SAP Version	Approval Date	Change	Rationale
		account for potential unequal residual variances with different group sizes.	
		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's advice.
		Added missing data at baseline will be imputed using MI approach under MAR assumption in Section 4.4.1.	Addition.
		Added adjustment for covariates and added appropriate baseline covariates for the binary targets in Section 4.5.1.2. Also suggested a missing data imputation for missing hypoglycemia incidence.	To implement FDA's advice.
		Added sensitivity analysis that considers all hypoglycemic events as one hypoglycemic event until a succeeding glucose value is ≥ 70 mg/dL in Section 4.6.3.1.1.1.	To implement FDA's feedback for SAP of the trial I8H-MC-BDCV.
		Added Section 4.6.4 analysis for device product complaints.	According to the new SAP template requirement
		Updated the subgroups for race in Section 4.7.2.	To implement FDA's advice.
		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's advice.
		Clarified the SAP language regarding the use unplanned measurements for post-baseline observations for HbA1c analysis in Section 4.1. Also clarified the SAP language for sensitivity analysis in Section 4.3.3.	To clarify based on FDA's advice.

Abbreviations: CGM = continuous glucose monitor; FDA = Food and Drug Administration (United States); PD = pharmacodynamics; PK = pharmacokinetics; P-R = persistent-recurrent; PSAP = program safety analysis plan;

1. Introduction

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

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To investigate the hypothesis that LY3209590 is noninferior to the comparator (insulin degludec) on glycemic control in study participants with T2D currently on basal insulin	• Change from baseline in HbA1c at Week 26
Key Secondary (Multiplicity Adjusted)	
• To demonstrate LY3209590 is superior to insulin degludec in the selected parameters of glycemic control	• Change from baseline in HbA1c at Week 26 • The event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 78 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured during the CGM session prior to Week 26
Other Secondary	
• To investigate the efficacy of LY3209590 compared with insulin degludec in additional parameters of glycemic control	• Change from baseline in HbA1c at Weeks 52 and 78 • Change from baseline in fasting glucose measured by SMBG at Weeks 26, 52, and 78 • Glucose variability measured during the CGM session prior to Weeks 26, 52, and 78 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured during the CGM session prior to Weeks 52 and 78 • Insulin dose at Weeks 26, 52, and 78
• To investigate the safety of LY3209590 compared with insulin degludec	• Incidence and rate of composite of Level 2 and 3 hypoglycemia events during treatment period • Body weight change from baseline to Weeks 26, 52, and 78 • Time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L) measured during the CGM session prior to Weeks 26, 52, and 78 • Time in hyperglycemia range defined as glucose >180 mg/dL (10.0 mmol/L) measured during the CGM session prior to Weeks 26, 52, and 78

Objectives	Endpoints
• To evaluate treatment impact between LY3209590 and insulin degludec based on patient-reported outcomes questionnaires	• Change from baseline in TRIM-D at Weeks 26, 52, and 78 • DTSQ change (DTSQc) from baseline at Weeks 26, 52, and 78
Tertiary	
• To investigate the treatment impact 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, 52, and 78 • Percentage of participants achieving HbA1c < 7% at Week 26 without nocturnal hypoglycemia during treatment phase up to Week 26 • Percentage of participants achieving HbA1c ≤ 6.5% at Weeks 26, 52, and 78 • Change from baseline in fasting serum glucose at Weeks 26, 52, and 78
	Safety: • Incidence and rate of Level 2 hypoglycemia events during treatment period • Incidence and rate of Level 3 hypoglycemia events during treatment period • Incidence of positive treatment-emergent antibody of LY3209590
	PK/PD: • LY3209590 PK and concentration-response relationships to key safety and efficacy measures • Potential intrinsic and extrinsic factors
	Patient-Reported Outcomes: • Change from baseline in SIM-Q at Week 26 • Frequency of responses to "Basal Insulin Experience: Likelihood of incorporating into routine" at Weeks 26 and 78 • Frequency of responses to "Basal Insulin Experience: Preference" at Weeks 26 and 78 • Change from baseline in EQ-5D-5L at Weeks 26, 52 and 78

Abbreviations: CGM = continuous glucose monitoring; DTSQc = Diabetes Treatment Satisfaction Questionnaire – Change Version; HbA1c = hemoglobin A1c; SIM-Q = Simplicity Questionnaire; SMBG = self-monitoring of blood glucose; T2D = type 2 diabetes; TRIM-D = Treatment-Related Impact Measure – Diabetes.

Primary Estimand (for primary objective)

US registration

The *primary* clinical question of interest is: What is the treatment difference between LY3209590 and insulin degludec in change from baseline to Week 26 (Visit 22) in HbA1c in study eligible participants with type 2 diabetes (T2D) currently on basal insulin regardless of treatment discontinuation for any reason and regardless of initiation of rescue medication?

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

Treatment Regimen Estimand Attribute	Description
Population	Targeted study population. See Section 3 for details
Endpoint	HbA1c change from baseline to Week 26.
Treatment condition	The randomized treatment regardless of treatment discontinuation and use of rescue medications.
Remaining intercurrent events	None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both addressed by the treatment condition of interest attribute.
Population-level summary	Difference in mean change between treatment conditions.

Abbreviations: HbA1c = hemoglobin A1c.

Rationale for estimand: The treatment regimen estimand estimates how participants with T2D are treated in clinical practice and takes into account both efficacy and safety.

Registration for other countries

The *primary* clinical question of interest is: What is the treatment difference between LY3209590 and insulin degludec in change from baseline to Week 26 (Visit 22) in HbA1c in study eligible participants with T2D currently on basal insulin and adherence to the randomized treatment without intercurrent events during the study treatment period?

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

Efficacy Regimen Estimand Attribute	Description
Population	Targeted study population. See Section 3 for details
Endpoint	HbA1c change from baseline to Week 26.
Treatment condition	The randomized treatment.
Remaining intercurrent events	None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both handled by the hypothetical strategy, for example, the potential outcome for those participants if the intercurrent events have not occurred will be estimated.
Population-level summary	Difference in mean changes between treatment conditions.

Abbreviations: HbA1c = hemoglobin A1c.

Rationale for estimand: The efficacy estimand supports the interpretation of the treatment effect from participants who adhere to study treatment and are 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 during the CGM session prior to Week 26 (Visit 22) will also use ***treatment regimen estimand*** for US registration and ***efficacy estimand*** for other countries.

The 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. Relative rate between randomized treatment groups will be used for treatment comparison.

1.2. Study Design

- Study BDCU is a Phase 3, multicenter, randomized, open-label, comparator-controlled study to evaluate the efficacy and safety of once-weekly basal insulin (LY3209590) compared to insulin degludec in participants with T2D treated with basal insulin.
- The study includes a 3-week screening/lead-in period, a 78-week treatment period, and a 5-week safety follow-up period.
- Participants will continue prior stable diabetes therapy with 0 to 3 allowed non-insulin antihyperglycemic medications during the study.
- Participants will discontinue their previous basal insulin doses at randomization and will be assigned to either LY3209590 or insulin degludec U100.
- Assignment to treatment groups will be determined by an interactive web-response system (IWRS). Participants will be randomly assigned to 1 of the 2 treatment groups in 2:1 ratio (LY3209590 : insulin degludec) at Week 0 (Visit 3). Stratification will be by country, HbA1c stratum at Week -3 (Visit 1) (<8.0%, ≥8.0%), and the type of basal insulin regimen at randomization (a. typical once-daily basal insulin; b. U-300 or BID regimens).
- This is a treat-to-target study, both treatment groups will undergo titration to achieve an FBG target within the range of 80-120 mg/dL. The primary endpoint at Week 26 (Visit 22) is based on participants reaching stable insulin dose by 8 to 12 weeks and glycemic stability in advance of the 26-week primary endpoint Hemoglobin A1c measure.
- 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

Primary Hypothesis

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control as measured by change from baseline to Week 26 (Visit 22) in HbA1c in participants with T2D currently on basal insulin. Thus, the null hypothesis (H_{01}) to be tested is the difference in the change from baseline to Week 26 (Visit 22) in HbA1c (LY3209590 – insulin degludec) is greater than the noninferiority margin (NIM). The 2-sided 95% confidence interval (CI) will be used for testing the noninferiority.

Secondary Hypotheses

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

- change from baseline in HbA1c at Week 26 (Visit 22)
  H_{02}: the difference (LY3209590 – insulin degludec) ≥ 0.0
- the event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment period up to Week 78 (Visit 37)
  H_{03}: the relative event rate (LY3209590 vs. insulin degludec) ≥ 1
- time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM collected during the CGM session prior to Week 26 (Visit 22)
  H_{04}: the difference (LY3209590 – insulin degludec) ≤ 0.0

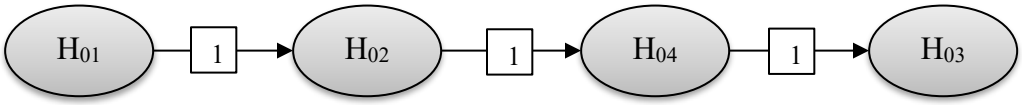
These hypotheses and the primary hypothesis will be tested using a strategy to control the overall type 1 error.

2.1. Multiplicity Adjustment

A graphical approach (Bretz et al. 2009; 2011) for multiple comparisons will be used to ensure the strong control of the overall type I error rate for testing the primary and key secondary (multiplicity adjusted) objectives. The overall significance level (α) will be set to 0.05. The total α will be used for the primary objective first, then the α will be allocated and transitioned to other key secondary objectives once the primary objective is met. Therefore, the noninferiority test for the primary objective will be based on the 2-sided 95% CI. Once the upper limit of the 2-sided 95% CI is below the NIM, the non-inferiority is achieved and the α of 0.05 will be distributed to 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 successfully. The NIM of 0.4% (for treatment regimen estimand) and 0.3% (for efficacy estimand) will both be tested to meet different regulatory requirements. No multiplicity adjustments will be made for conducting separate analyses relative to the treatment regimen and efficacy estimands. Each estimand will have its own familywise error rate of 0.05.

Approved on 27 May 2024 GMT

For primary and key secondary efficacy objectives, the details of type I error control strategy are illustrated in the figure :



Both treatment regimen estimand and efficacy estimand will be used to assess these objectives. As they are intended for different purposes, no multiplicity adjustments will be made for conducting separate analyses relative to the treatment regimen estimand and efficacy estimands. In addition, no multiplicity adjustments will be made for evaluating other secondary and exploratory objectives, or for safety assessments.

3. Analysis Sets

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

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

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.

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 treatment regimen estimand, EAS1 will be used. For efficacy estimand, other secondary and tertiary efficacy measures, EAS2 will be used (using the data up to the intercurrent events). The treatment comparison will be based on either 2-sided test or 95% CI.

Unless otherwise noted, the safety analyses will be conducted on the Safety Analysis set (SS, see the definition in Section 3). Percentages will be calculated using the 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, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. For certain variables that are considered to be log-normally distributed, the geometric mean and coefficient of variation (CV) will be provided instead. Either the mixed model repeated measurement (MMRM) model or the analysis of covariance (ANCOVA) model will be used to analyze continuous outcomes. Least-squares (LS) means, and standard errors derived from the analysis models will also be displayed. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons. For certain safety laboratory measures, log-transformed values will be analyzed in the statistical model instead. The actual, change from baseline and percentage change from baseline will be presented using the derivation based on the output from the statistical model and the assumption of lognormality.

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

In this study, the negative binomial regression will be used to analyze the number of hypoglycemic episodes. Group Mean instead of LS mean will be estimated and delta method will be used to estimate the standard error of the Group Mean (Qu and Luo 2015). Group Mean is defined as the mean response in the treatment group for the studied population. The difference between LS mean and the Group Mean is that LS mean estimates the response by taking the inverse link function on mean covariates, while the Group Mean takes the inverse link function on individual patient covariates first and then averages over all patients. For analysis of hypoglycemia, the empirical method based on exposure adjusted rate (calculated by total number

of events divided by total exposure) may be used for the treatment comparison if the number of episodes is too small and leads to convergency issues in the negative binomial regression model.

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

Analysis	Baseline Observations	Post-Baseline Observations
HbA1c (treatment regimen estimand)	The baseline is the last non-missing assessment prior to or on the first day of study treatment.	Planned measurements at primary and secondary endpoints Weeks 26, 52, 78 (Visits 22, 30, 37) in EAS1. Use unplanned measurements (on the same visit day) if no planned measurement. Multiple imputation approach will be used to impute missing observations at these endpoint visits.
HbA1c (efficacy estimand)	The baseline is the last non-missing assessment prior to or on the first day of study treatment.	Weeks 2, 4, 12, 16, 26, 36, 52, 64 and 78 (Visit 5, 7, 15, 17, 22, 25, 30, 32, and 37) in EAS2 for MMRM. All planned measurements at scheduled visits will be included. Use unplanned measurements (on the same visit day) if no planned measurement.
CGM parameters (treatment regimen estimand)	The baseline will be derived from the data collected during CGM session prior to the first dose date of study treatment. Multiple imputation will be used to impute missing observations at baseline.	The CGM sessions prior to Week 26, 52, 78 (Visit 22, 30, 37) in EAS1 Multiple imputation approach will be used to impute missing observations at these sessions.
CGM parameters (efficacy estimand)	The baseline will be derived from the data collected during CGM session prior to the first dose date of study treatment.	The CGM sessions prior to Weeks 4, 12, 26, 52, 78 (Visit 7, 15, 22, 30, 37) in EAS2 for MMRM
Insulin dose during the treatment period	The baseline period is the lead-in period prior to the initiation of study treatment. The following variables will be derived: • daily dose in U • weekly dose in U • dose in U/kg/day The detailed description is added in Section 4.4.2.1.	All scheduled visits between Week 0 (Visit 3) and Week 78 (Visit 37) in EAS2 for MMRM. The following variables will be derived: • daily dose in U • weekly dose in U • dose in U/kg/day The detailed description is added in Section 4.4.2.1.

Analysis	Baseline Observations	Post-Baseline Observations
Fasting glucose by SMBG	The baseline period is the lead-in period up to the first day of study treatment. The average of all Fasting SMBG during Visit 2 date and on or prior to the first day of study treatment will be considered as baseline. - For treatment regimen estimand, multiple imputation will be used to impute missing observations at baseline for treatment regimen estimand.	Data will be summarized for each visit as an average of all Fasting SMBG from the time after the prior visit and up to that day of the visit. - For treatment regimen estimand, measurements at Weeks 26, 52, 78 (Visits 22, 30, 37) in EAS1 for ANCOVA. Multiple imputation approach will be used to impute missing observations at these endpoint visits. - For efficacy estimand all available data after the day of first dose of study treatment up to Week 78 (Visit 37) in EAS2 for MMRM.
Fasting Serum Glucose by central lab	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 for treatment regimen estimand.	All planned measurements at scheduled visits will be included. - For treatment regimen estimand, measurements at Weeks 26, 52, 78 (Visits 22, 30, 37) in EAS1. Multiple imputation approach will be used to impute missing observations at these endpoint visits. - For efficacy estimand all scheduled visits after the day of first dose up to Week 78 (Visit 37) in EAS2 for MMRM.
Participant-reported hypoglycemia	The baseline period is the screening/lead-in period prior to the first day of study treatment.	• Treatment period starts on the first day of study treatment and ends on Week 78 (Visit 37), if study completed treatment or on the last dose date of study treatment + 10 days and +1 day for LY3209590 and Insulin Degludec, respectively, if discontinued study treatment early. • Post-treatment period starts from end of Treatment period +1 day and ends on the last day in the study

Analysis	Baseline Observations	Post-Baseline Observations
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).	Safety analysis period starts after the first dose(AE Start Relative to Exposure Assessment in CRF is used to determine) and ends at the last visit in the study including safety follow-up period. Note: An AE will be TEAE if reported to be worsen in severity from baseline.
Safety laboratory tests, vital signs and body weight	The baseline will be the last non-missing assessment prior to or on the first day of study treatment. Planned measurements at scheduled visits will be included.	All scheduled visits after the first day of study treatment up to follow-up Visit 802 for MMRM and/or ANCOVA. Planned measurements at scheduled visits will be included.
Elevated or low: Laboratory values, vital signs, and body weight categorical measures	Starts from the screening visit and ends prior to or on the first day of study treatment. All available scheduled and unscheduled measurements will be included. The baseline for weight will be the last non-missing value during the baseline period.	Starts after the day of study treatment and ends at the last visit in the study including both treatment period and follow-up period. All available scheduled and unscheduled measurements in the specified analysis period will be included.
Anti-LY3209590 antibody	Refer to PSAP.	Refer to PSAP.
Patient-reported outcomes	The baseline will be the data collected at Week 0 (Visit 3).	• All scheduled visits after Week 0 (Visit 3). • Last collection after Week 0 (Visit 3).

Abbreviation: AE = adverse event; ANCOVA = analysis of covariance; CGM = continuous glucose monitoring; CRF = case report form; EAS1 = efficacy analysis set 1; EAS2 = efficacy analysis set 2; HbA1c = hemoglobin A1c; MMRM = mixed model repeated measurement; 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.

The number and percentage of participants who have completed or discontinued from the study or treatment will be summarized by treatment using the Randomized Population. The individual reasons for discontinuation will also be included in the summary. Comparison between LY3209590 and Insulin Degludec will be conducted using the Fisher's exact test.

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

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

4.3. Primary Endpoint Analysis

4.3.1. Definition of Endpoint

The primary endpoint of this study is the HbA1c change from baseline to Week 26 (Visit 22). The HbA1c is reported in unit of % by central laboratory and will be converted to the unit of mmol/mol using the following formula: HbA1c in mmol/mol = 10.93 * HbA1c in % - 23.5 (http://www.ngsp.org/ifccngsp.asp). The HbA1c analysis will be conducted for both units.

4.3.2. Main Analytical Approach

The primary objective is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control in the targeted study population. The noninferiority test will be based on: ***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 non-missing baseline measure	All participants in EAS2 with non-missing baseline measure and at least one non-missing post-baseline scheduled measure
Analysis Data	All non-missing observations at baseline and Week 26 (Visit 22) regardless of the use of study intervention or rescue medications.	All non-missing observations at baseline and all scheduled post-baseline timepoints during treatment period (that is, Weeks 2, 4, 12, 16, 26, 36, 52, 64 and 78) prior to the date of last study dose + 10 days for LY3209590 and +1 day for Insulin Degludec, or the initiation of rescue medication whichever is earlier (for participants with an intercurrent event).
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 in the same treatment arm. If there are only a limited number of retrieved participants (i.e., at least 1 arm has less than 8 participants who discontinued study treatment early and who have endpoint visit measurements) or the model cannot converge, the missing HbA1c at	There may be missing values due to the early discontinuation of study intervention or use of rescue medication. The MMRM model will be used, and the missing values will be handled in the MMRM analysis under the assumption of missing at random.

	Treatment Regimen Estimand	Efficacy Estimand
	Week 26 will be imputed by return-to-baseline multiple imputation approach (Qu and Dai 2022).	
Analysis Model	After the imputation, the observed and imputed data will be analyzed by the ANCOVA model using treatment, strata (country, and the type of basal insulin at randomization), and baseline value of the dependent variable as independent variables. The statistical inference will be based on the multiple imputation framework by Rubin (1987).	The MMRM model will include treatment, strata (country, and the type of basal insulin at randomization), visit and treatment-by-visit interaction as fixed effects, and baseline of the dependent variable as a covariate. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for the MMRM models. An unstructured covariance structure will be used to model the within-participant errors. If this structure fails to converge, the following covariance structures will be used in order until one converges: 1. Toeplitz with heterogeneity 2. autoregressive with heterogeneity 3. compound symmetry with heterogeneous variances 4. Toeplitz 5. Autoregressive 6. compound symmetry without heterogeneous variances.

Abbreviation: ANCOVA = analysis of covariance; EAS1 = Efficacy Analysis Set 1; EAS2 = Efficacy Analysis Set 2; HbA1c = hemoglobin A1c; MMRM = mixed model repeated measurement.

The 2-sided 95% CI of the LS mean difference (LY3209590 – insulin degludec) in the HbA1c change from baseline to Week 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 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

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 penalties are added. The multiple imputation framework by Rubin (1987) will be used to summarize the results. The corresponding p-values of non-inferiority test will be shown by color scale in the figure.

Imputation under the noninferiority null hypothesis

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 of LY3209590 group only. The ANCOVA model for treatment regimen estimand will rerun using the adjusted data. The multiple imputation framework by Rubin (1987) will be used to summarize the results.

Including Inadvertently Enrolled Participants

The primary efficacy analysis will be repeated for the mITT population, including participants inadvertently enrolled, for both treatment regimen estimand and efficacy estimand.

Assuming unequal variances due to different group sizes

A sensitivity analysis will be performed on the treatment regimen estimand, using the same ANCOVA model described in Section 4.3.2 but assuming unequal variances to account for potential unequal residual variances due to different group sizes.

4.3.4. Supplementary Analyses

Additional analysis may be conducted as needed.

4.4. Secondary Endpoints Analysis

4.4.1. Key Secondary Endpoints

A graphical approach (see Section 2.1) will be used to control the overall type I error for the primary objective and the key secondary objectives. The key secondary objectives will test the superiority of LY3209590 compared with insulin degludec for the following endpoints:

1) change from baseline in HbA1c at Week 26 (Visit 22);
2) the event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during the treatment period up to Week 78 (Visit 37); and
3) time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive collected during the CGM session prior to Week 26 (Visit 22).

4.4.1.1. Definition of Endpoint(s)

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

The hypoglycemia events will be based on participant entry into an e-diary which receives all blood glucose (BG) measurements performed by the participant and transmitted via Bluetooth from the study-provided glucometer. The nocturnal period is defined by midnight to 6 AM. The event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) will be based on the count of the hypoglycemia episodes in the nocturnal period and the corresponding exposure of study intervention.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive will be based on the percentage of CGM readings within the glucose range during the specific CGM session. The derivation of CGM parameters is provided in Appendix 6 (Section 6.6).

4.4.1.2. Main Analytical Approach

The 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 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.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM will be analyzed using an ANCOVA model for treatment regimen estimand and an MMRM model for efficacy estimand. The analyses are similar to the primary analysis described in Section 4.3.2 with additional term of baseline HbA1c stratum (<8.0%, ≥8.0%) in analysis models. For treatment regimen estimand, For the treatment-regimen estimand, only participants with an observation either 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 and at Week 26 (Visit 22) the missing data will be imputed by multiple imputation with the approach similar to the imputation used for the primary endpoint.

4.4.1.3. Sensitivity Analysis

The analysis (in Section 4.4.1.2) will be repeated for mITT population, including participants inadvertent enrolled, for both treatment regimen estimand and efficacy estimand. For the time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM, a sensitivity analysis will be performed on the treatment regimen estimand, using the same ANCOVA model described in Section 4.3.2 but assuming unequal variances in order to account for potential unequal residual variances due to different group sizes.

4.4.2. Supportive Secondary Endpoints

4.4.2.1. Other Efficacy Endpoints

The analysis of continuous efficacy measures of change from baseline for:

- HbA1c at Weeks 52 and 78 (Visits 30 and 37),
- fasting glucose by SMBG at Weeks 26, 52 and 78 (Visits 22, 30 and 37), and
- CGM (selected) parameters at the 4-week sessions prior to Weeks 26, 52 and 78 (Visits 22, 30 and 37)

will be based on both treatment regimen estimand and efficacy estimand. Analysis of insulin dose will be based on efficacy estimand only.

For treatment regimen estimand, only participants with an observation either 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 except analysis of HbA1c.

For efficacy estimand, participants with baseline and at least one post baseline observation will be included in the analysis. The longitudinal observations of actual and change from baseline in HbA1c up to Week 78 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%). A compound symmetry covariance structure will be used to model the within-participant errors for fasting glucose from SMBG and insulin dose.

Additional analysis 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 session. Section 6.6 (Appendix 6) provides the derivation of CGM parameters .

Longitudinal logistic regression model with independent variables of treatment, strata (country, the type of basal insulin at randomization, and, baseline HbA1c stratum), visit and treatment-by-visit interaction and baseline of the dependent variable will be used to analyze CGM targets of glycemic controls (see Section 6.6.1). Same order of variance-covariance structures will be used as mentioned for MMRM in Section 4.3.2 for selection.

The time point for primary CGM data analysis is CGM session. In addition, the average time in glucose range, hypoglycemia range and hyperglycemia range by week (by visit for treatment period) will be summarized by treatment. Average daily time since last dose by CGM Session during treatment period will also be summarized for LY3209590.

Missing data patterns will be summarized at daily, weekly (visit) and CGM session levels.

4.4.2.1.2. Study Insulin Dose Analysis

For study insulin dose, the average daily dose in U, weekly dose in U and daily dose in U/kg during each visit for individual participants will be used in the analysis.

In the LY3209590 group,

- the average dose of each visit (that is, average of weekly doses since last visit) will be used as the average weekly dose in U;
- the average daily dose in U will be the average weekly dose in U divided by 7;
- the average daily dose in U/kg will be the average daily dose in U divided by body weight for the visit.

In the insulin degludec group,

- the average dose of each day within a visit (that is, average of each day doses since last visit) will be used as the average daily dose in U;
- the average weekly dose in U will be calculated by the average daily dose in U multiplied by 7;
- the average daily dose in U/kg will be the average daily dose in U divided by last measured body weight on or prior to the visit.

For participants using typical once-daily pre-study basal insulin, the average pre-study basal dose during the lead-in period will be the baseline daily dose in U. For participants using pre-study U-300 or NPH BID, the average pre-study basal dose during the lead-in period multiplied by 0.8 will be the baseline daily dose in U. The baseline daily dose in U multiplied by 7 will be the baseline weekly dose in U for the study insulin dose analysis. The baseline daily dose in U divided by baseline weight will be the baseline daily dose in U/kg.

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

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

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

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

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

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

Summary statistics for the transformed scores of each domain and all domains 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, and the type of basal insulin at randomization, baseline HbA1c stratum), and baseline value of the dependent variable as independent variables.

4.4.2.3.2. Diabetes Treatment Satisfaction Questionnaire (DTSQ)

Diabetes Treatment Satisfaction Questionnaire-Status (DTSQs)

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 T2D. The DTSQs consists of 8 items that assess treatment satisfaction as well as concerns about hyperglycemia and hypoglycemia over the past few weeks, prior to the visit. Each item is rated on a 7-point Likert scale. Items 1 and 4-8 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, and 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 DTSQs is planned prior to the initiation of study treatment. The total scores of Item 1 and 4-8 and the individual scores of Items 2 and 3 will be summarized. Wilcoxon rank-sum test will be used for treatment comparison.

Diabetes Treatment Satisfaction Questionnaire-Change (DTSQc)

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 and 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 4-8 are summed to obtain a total treatment satisfaction score ranging from -18 to 18. Items 2 and 3 are scored individually.

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

4.5. Tertiary Endpoint Analysis

4.5.1. Tertiary Efficacy Endpoints

4.5.1.1. Fasting Serum Glucose

Fasting serum glucose (FSG), measured by central laboratory, will be analyzed (for both international units [SI] and conventional units [CN]) for both treatment regimen estimand and efficacy estimand using same ANCOVA (at Weeks 26, 52 and 78) and MMRM model (at all scheduled visits), respectively as described in Section 4.3.2 with an additional term of baseline

HbA1c stratum (<8.0%, ≥8.0%), using data from EAS1 and EAS2, respectively. Missing data imputation and analysis set will be the same as described in Section 4.4.2.1.

4.5.1.2. Binary outcomes for HbA1c target

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 the specified timepoints regardless of the use of study intervention or rescue medications.
Endpoint	1) HbA1c target (< 7% or ≤ 6.5%) at the specified timepoints; 2) The composite of a) binary outcome of HbA1c <7% at Week 26, and, b) binary outcome of no nocturnal level 2 or 3 hypoglycemia during treatment phase up to Week 26. 3) The composite of a) binary outcome of HbA1c <7% at Week 26, and, b) binary outcome of no level 2 or 3 hypoglycemia during treatment phase up to Week 26 with "Yes" indicating achieving the target (in respective endpoints defined above).
Missing Data	1) For HbA1c, missing values at the specified timepoints will be imputed using the same method for the primary endpoint (Section 4.3.2). 2) For hypoglycemia that are included in the composite endpoints, a participant who discontinued both treatment and treatment period before Week 26 (Visit 22) is considered as a non-responder (i.e. experienced the event).
Analysis Model	These endpoints will be analyzed using a logistic regression model including - independent variables of treatment, - strata (country, and the type of basal insulin at randomization), - baseline HbA1c value - additionally, *for the composite endpoint* o baseline incidence of hypoglycemia and, o interaction term of baseline HbA1c value * 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 1: 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.

4.5.3. Tertiary Patient Reported Outcomes

4.5.3.1. EQ-5D-5L

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

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

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

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

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

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

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

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

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

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

4.5.3.3. Basal Insulin Experience

Likelihood of incorporating into routine

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

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

Preference

This is a Lilly-developed, participant-completed question to understand the participant's preference for their pre-study 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 and using Wilcoxon rank sum test for treatment comparison.

4.6. Safety Analyses

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

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

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

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

4.6.1. Extent of Exposure

Duration of exposure to study treatment will be summarized. No p-values will be reported in these tables as they are intended to describe the study populations, rather than test hypotheses about them.

Total patient-years of exposure will be reported. The number and proportion of participants falling into the following different exposure categories will also be summarized by study treatment:

- >0, ≥30 days, ≥90 days, ≥180 days, ≥365 days, ≥545 days, and
- >0 and < 30 days, ≥30 and < 90 days, ≥90 and <180 days, ≥180 and < 365 days, ≥365 and <545 days, ≥545 days.

Exposure on study treatment will be calculated as:

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

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

All participants who complete the study treatment period are required to complete a safety follow-up period and participants who discontinue the study treatment prematurely are encouraged to remain in the study for safety monitoring. The duration on study from the first dose of study treatment to the study disposition (defined as treatment period disposition or follow up disposition, whichever is later)date will also be summarized by treatment.

A listing of exposure to study treatment and time in study since first dose will be provided.

4.6.2. Adverse Events

Events that are newly reported after the first dose of investigational product (IP) or reported to worsen in severity from baseline will be considered treatment emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period (see the table in Section 4.1) will be used as baseline severity.

The table below describes the analysis related to AEs.

Analysis	Details
Overview of AEs	Number and percentage of participants who experienced: • SAE • Death • Discontinuation from study treatment due to an AE • Discontinuation from study due to an AE • TEAE • TEAE related to study treatment

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

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

4.6.2.1. Safety topic of Interest

4.6.2.1.1. Severe Hypoglycemia

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

A summary of severe hypoglycemia by PT in decreasing order of risk difference (LY3209590 – insulin Degludec) will be provided. The incidence and event rate during the treatment period will be analyzed using the method described in Section 4.6.3.1. A listing of severe hypoglycemia events will also be provided.

4.6.2.1.2. Persistent-Recurrent Hypoglycemia

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

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

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

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

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

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

4.6.2.1.3. Systemic Hypersensitivity Reactions

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

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

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

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

Individual PTs that satisfied the query will appear in the summary nested within each SMQ in decreasing order of risk difference (LY3209590 – insulin Degludec).

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

4.6.2.1.4. Injection Site Reactions

Injection site reactions (ISR) are AEs localized to the immediate site of the administration of a medication. The evaluation of ISRs will be through the unsolicited reporting of ISR TEAEs and through the use of an Injection Site Reaction Follow-up Form completed by the investigator for each incidence of ISR.

A summary of the number of participants with reported events meeting any of the following categories will be provided:

- MedDRA HLT of Injection site reactions,
- MedDRA HLT of Administration site reactions NEC,
- Lipodystrophies and localized amyloidosis, as represented by PTs of:
    - lipoatrophy,
    - lipodystrophy acquired,
    - partial lipodystrophy,
    - lipohypertrophy,
    - sclerema, and
    - cutaneous amyloidosis.

The summary will present the number of participants who reported:

- at least one AE meeting any of the above categories,
- any AE in each category, and
- 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 (LY3209590 – insulin Degludec).

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 MedDRA narrow search for the following SMQ:

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

A summary will present:

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

The PTs will be listed for summary within each SMQ in decreasing order of risk difference (LY3209590 – insulin Degludec).

4.6.2.1.6. Diabetic Ketoacidosis (DKA)

The 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 in decreasing order of risk difference (LY3209590 – insulin Degludec).

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

The diabetic retinopathy or maculopathy will be searched by MedDRA PTs from all TEAEs. The list of PTs for the search is provided in Appendix 7 (Section 6.7). A summary of treatment-emergent retinopathy or maculopathy by PT in decreasing order of risk difference (LY3209590 – insulin Degludec) will be provided.

4.6.2.1.8. Peripheral Edema

The peripheral edema will be searched by MedDRA PTs (see Section 6.8) from all TEAEs. The number and percentage of participants experiencing treatment-emergent peripheral edema will be summarized by PT in decreasing order of risk difference (LY3209590 – insulin Degludec)..

4.6.2.1.9. Hypokalemia

The TEAEs of hypokalemia will be identified by narrow terms in Hypokalaemia SMQ (20000233). A summary of the number of participants with reported treatment-emergent events meeting the SMQ narrow search criteria by PT in decreasing order of risk difference (LY3209590 – insulin Degludec) will be provided.

4.6.2.1.10. Hyperglycemia

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

4.6.2.1.11. Major Adverse Cardiovascular Events (MACE)

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

- death
- Cardiac ischemic events (including *myocardial infarction* or *hospitalization for unstable angina*)
- cerebrovascular events (including *stroke* or *Transient Ischemic Attack [TIA]*)
- hospitalization for heart failure, and
- coronary revascularization procedure

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

4.6.2.1.12. Medication Error of Interest

Medication Errors of Interest (MEI) are defined as medication error adverse events (SMQ 20000224 - narrow and broad terms) that meet the criteria of important protocol deviations (IPD), according to the Trial Issue Management Plan (TIMP) and are indicative of multiple doses. These events are considered important protocol deviations because of their potential to impact participant's safety. For this same reason, these events are considered of special interest among all medication error AEs reported in the trial.

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

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

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

4.6.3. Additional Safety Assessments

4.6.3.1. Hypoglycemic Events

4.6.3.1.1. Participant-Reported Hypoglycemic Events

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

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

A set of Level 1 and Level 2 hypoglycemia events will be identified based on blood glucose reading values reported in the participant e-diary. A Level 3 hypoglycemia event is only confirmed by investigator and may not have an associated blood glucose reading.

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

- earliest date time and
- minimum glucose value, if applicable
- maximum severity (Level 1, 2 or 3)
- combining all symptoms and outcomes 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.

Further, all episodes will be classified as nocturnal (occurs between midnight and 0600) or non-nocturnal (occurs between 0600 and midnight) hypoglycemia by the time of the originating event.

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 evaluation of potential persistent/recurrent hypoglycemia events will be through assessment of the clinically significant events confirmed by investigators based on clinical judgment and through events identified by pre-specified criteria (see Section 4.6.2.1.2 and Appendix 9 [Section 6.9] for details) using information based on the participant-reported hypoglycemia.

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

Endpoint	Analysis Period	Statistical Method [a]
Event rate of Level 1 hypoglycemia events (events/participant/year): • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 0-78, 12-26, 26-52, 26-78, 52-78 weeks, post-treatment period	Negative binomial regression with treatment, baseline HbA1c and baseline Level 1 hypoglycemia rate as covariates, log (exposure/365.25 days) as the offset in the model.
Event rate of Level 2 hypoglycemia events (events/participant/year): • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 0-78, 12-26, 26-52, 26-78, 52-78 weeks, post-treatment 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.
Event rate of Level 3 hypoglycemia events (events/participant/100 year): • All documented	Baseline, 0-26, 0-52, 0-78, 26-52, 26-78, 52-78 weeks, post-treatment period	Negative binomial regression with treatment and baseline HbA1c and baseline Level 3 hypoglycemia rate as covariates, log (exposure/365.25 days) as the offset in the model. If the number of events is too small to run the negative binomial regression, exposure adjusted rate calculated by total number of events divided by total exposure for individual patients will be provided and the empirical method (see Appendix 9 [Section 6.9] for details) will be used for treatment comparison.
Event rate of Level 2/3 hypoglycemia events (events/participant/year): • All documented • Nocturnal • Non-nocturnal	Baseline, 0-6, 0-12, 0-26, 0-52, 0-78, 12-26, 26-52, 26-78, 52-78 weeks, post-treatment period	Negative binomial regression with treatment, baseline HbA1c and baseline hypoglycemia rate of the same hypoglycemia type as covariates, 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 (2003).
Incidence of Level 1 hypoglycemia events: • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 0-78, 12-26, 26-52, 26-78, 52-78 weeks, post-treatment period	Logistic regression with treatment, baseline HbA1c and baseline Level 1 hypoglycemia incidence as covariates.
Incidence of Level 2 hypoglycemia events: • All documented	Baseline, 0-6, 0-12, 0-26, 0-52, 0-78, 12-26, 26-52, 26-78, 52-78 weeks, post-treatment period	Logistic regression with treatment, baseline HbA1c and baseline Level 2 hypoglycemia incidence as covariates.
Incidence of Level 3 hypoglycemia events: • All documented	Baseline, 0-26, 0-52, 0-78, 26-52, 26-78 , 52-78 weeks, post-treatment period	Logistic regression with treatment and baseline HbA1c as covariates.

Endpoint	Analysis Period	Statistical Method [a]
Incidence of Level 2/3 hypoglycemia events: • All documented • Nocturnal • Non-nocturnal	Baseline, 0-6, 0-12, 0-26, 0-52, 0-78, 12-26, 26-52, 26-78, 52-78 weeks, post-treatment 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 • identified by a pre-specified criteria	Safety analysis period (see definition in Section 4.6)	The number of participants with at least one event will be summarized and compared by Fisher's exact test. The number of events will also be provided. Listings of the events will also be provided.

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

Notes: The yearly hypoglycemia rate during defined period is calculated by the number of hypoglycemia within the period/number of days patient at risk within the period*365.25. For rare events, 100 year rate will be provided.
The hypoglycemia incidence during defined period indicates if the patient has at least 1 hypoglycemia events within the period (Yes/No).
Group comparisons for hypoglycemia incidence and rate at baseline, baseline HbA1c is not included in the model.
The hypoglycemia rate during the defined period is calculated by the number of hypoglycemia events within the period/number of days a participant is at risk within the period. The hypoglycemia incidence during the defined period indicates if the participant has at least 1 hypoglycemia event within the period (yes/no).

A sensitivity analysis will be performed for selected hypoglycemic endpoints using an alternative definition of continuation of hypoglycemic events. Hypoglycemic events will be considered one hypoglycemic episode until a succeeding glucose value is ≥ 70 mg/dL. All such events will be combined into a single episode with the same attributes as defined earlier in this section.

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 Section 6.6.2. Missing data will be handled as described in Appendix 6 (Section 6.6). The analysis for incidence, event rate, and duration are described in the table below:

Endpoint	Analysis Period	Statistical Method
Event rate of hypoglycemia events (24-hour Period) in events/participant/year: • Level 1 or Level 2 • Level 2 • Level 2 hypoglycemic events ending with BG ≥70 mg/dL	Baseline, 0-4, 8-12, 22-26, 48-52, 74-78 weeks, follow-up period	Negative binomial regression with treatment, baseline HbA1c and baseline event rate of the corresponding level of hypoglycemia as covariates, log (exposure/365.25 days) as the offset in the model.

Endpoint	Analysis Period	Statistical Method
Incidence of hypoglycemia events (24-hour Period): • Level 1 or Level 2 • Level 2 • Level 2 hypoglycemic events ending with BG ≥70 mg/dL	Baseline, 0-4, 8-12, 22-26, 48-52, 74-78 weeks, follow-up period	Logistic regression with treatment, baseline HbA1c and baseline incidence of the corresponding level of hypoglycemia as covariates.
Duration of hypoglycemic events (24-hour Period) in minutes: • Level 1 or Level 2 • Level 2 • Level 2 hypoglycemic events ending with BG ≥70 mg/dL	Baseline, 0-4, 8-12, 22-26, 48-52, 74-78 weeks, follow-up period	**For individual CGM sessions (0-4, 8-12, 22-26, 48-52, 74-78 weeks):** MMRM model with treatment, strata (country, baseline HbA1c stratum and the type of basal insulin at randomization), session and treatment-by- session interaction as fixed effects, and baseline duration of the corresponding level of hypoglycemic events as a covariate. **For Baseline and Follow-up period:** ANOVA models only include treatment as covariate.

Abbreviations: ANOVA = Analysis of covariance; CGM = Continuous Glucose monitor; HbA1c = glycated hemoglobin; MMRM = mixed model for repeated measures.

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

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 reported Level 2 hypoglycemia episodes will be summarized for each CGM session.

A listing will be provided for participants with Level 2 hypoglycemia episodes lasting more than 360 minutes.

4.6.3.2. Laboratory and Adverse Event for Hepatic Safety

Hepatic labs include:

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

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

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

Analysis	Details
Abnormal postbaseline categories – hepatic safety parameters	ALT: The number and percentage of participants with a measurement greater than or equal to 1 time (1×), 3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. AST: The number and percentage of participants with a measurement greater than or equal to 1 time (1×), 3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. ALP: The number and percentage of participants with a measurement greater than or equal to 2 times (2×) and 3 times (3×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. TBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2×), 5 times (5×), and 8 times (8×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. DBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2×) and 5 times (5×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value. GGT: The number and percentage of participants with a measurement greater than or equal to 2 times (2×) the performing laboratory ULN during the postbaseline period will be summarized for all participants with a postbaseline value.
Treatment-emergent potentially drug-related hepatic disorders	Potentially drug-related hepatic disorders are defined using a custom query based on the following SMQs: • Broad and narrow terms in the Liver-related investigations, signs and symptoms SMQ (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009) • Broad and narrow terms in the Hepatitis non-infections SMQ (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013) • 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. Dashed lines represent TBL and transaminase cutoffs of 2× ULN and 3× ULN, respectively. A potential Hy's law case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2× ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3× ULN, without cholestasis (defined as ALP less than 2× ULN).
Hepatocellular drug-induced liver injury screening table	The percentages of study participants falling in each of the 3 relevant quadrants of the plot (right upper, left upper, right lower) will be summarized in a table.
Cholestatic drug-induced liver injury screening plot (TBL vs ALP)	Each participant's data is plotted based on their maximum postbaseline TBL (y-axis) and ALP (x-axis), regardless of the time between the 2 maximum values. Lines represent TBL and ALP cutoffs of 2× ULN and 3× ULN, respectively. A potential cholestatic liver injury case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2× ULN within 30 days after maximum postbaseline ALP equal to or exceeding 3× ULN.
Cholestatic drug-induced liver injury screening table	The percentages of study participants falling in each of the 3 relevant quadrants of the plot (right upper, left upper, right lower) will be summarized in a table.
List of Participants with potential hepatocellular drug-induced liver injury	Includes participants falling in the right upper quadrant in the Hepatocellular Drug-Induced Liver Injury Screening plot Variables to include are unique subject ID, age, sex, race, treatment, max AST, max ALT, max ALP, max TBL
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 Variables to include are unique subject identifier, age, sex, race, treatment, max AST, max ALT, max ALP, max TBL

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, direct bilirubin and total bilirubin, and
- lipid measures: triglycerides, total cholesterol, LDL-C, and HDL-C (results from fasting samples).

MMRM model (as described in Section 4.6) will be used for the observed values, change from baseline and percentage change from baseline, for which log-transformation will be applied.

Geometric LS means will be provided. Analyses will be provided in both international units (SI) and conventional units (CN) if they are different.

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

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

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

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

Scatter plots of baseline 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. ADaM datasets will include variables to enable the creation of scatter plots for use in either an interactive tool or for ad-hoc figures.

4.6.3.4. Vital Signs and Physical Characteristics

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

Analysis Type	Analysis Details
Observed values and change by visit	• Includes all participants in the Safety Analysis Set who have both a baseline and at least 1 postbaseline observation. • MMRM model (as described in Section 4.6) will be used. See also: Table 6.2 from the Analyses and Displays for Labs white paper (PHUSE 2022)
Summary by category	• Definitions provided in Tables 31-33 from FDA's September 2022 Standard Safety Tables and Figures document will be used for the numerator. o Systolic BP (mm Hg): Level 1 (low): <90, Level 1 (high): ≥90, Level 2 (high): ≥120, Level 3 (high): ≥140, Level 4 (high): ≥160, Level 5 (high): ≥180 o Diastolic BP (mm Hg): Level 1 (low): <60, Level 1 (high): >60, Level 2 (high): >90, Level 3 (high): >110, Level 4 (high): ≥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: o (Loss) decrease: Level 1: ≥5%, Level 2: ≥10%, Level 3: ≥20% o (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.

***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.

4.6.3.5. Device Product Complaints

A summary and/or listing, as appropriate, 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 (TE) Anti-Drug Antibody (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 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.

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

4.7.2. Subgroup analyses

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

4.7.2.1. Subgroup analysis for HbA1c

The subgroups, for analyzing HbA1c and change in HbA1c from baseline to Week 26, will be defined as:

- baseline HbA1c stratum (<8.0% and ≥8.0%);
- type of pre-study basal insulin (typical once-daily basal insulin and U-300/ NPH BID regimens);
- region (US and non-US);
- region (North America, South America, Europe, Asia);
- age (<65 years and ≥65 years);
- gender (Female and Male);
- ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and, White);
- number of Non-Insulin Antihyperglycemic Medications at baseline (≤1 and >1);
- estimated Glomerular Filtration Rate (eGFR) at baseline (<60, ≥60 to <90 and ≥90); and
- duration of diabetes per medical history (< median and ≥ median).

A subgroup category with less than 10 participants will not be included in the analysis.

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 13 [Section 6.13]).

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

4.7.2.2. Subgroup analysis for Participant-Reported Hypoglycemic Events

The subgroups, for analyzing documented Level 2/3 hypoglycemia, non-nocturnal and nocturnal hypoglycemia rates during 0-78 weeks, will be defined as:

- baseline HbA1c stratum (<8.0% and ≥8.0%);

- type of pre-study basal insulin (typical once-daily basal insulin and U-300/NPH BID regimens);
- age (<65 years and ≥65 years);
- region (US and non-US);
- region (North America, South America, Europe, Asia); and
- estimated glomerular filtration rate (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), 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 DMC will be responsible for reviewing unblinded data during the study. The committee will include 4 clinicians and 1 statistician who are independent experts not involved in the study. The DMC will review unblinded safety data to ensure the safety of study participants and some efficacy data to confirm a reasonable risk-benefit profile. A subset of analyses described above in Sections 4.3 to 4.6 will be provided for the DMC review. The external Statistical Analysis Center statistician/analyst will generate the unblinded reports and confidentially distribute the unblinded reports to DMC members. Study team will remain blinded to study treatment until the planned unblinding occurs. The DMC will be conducted to maintain study integrity. Details of DMC is included in the DMC charter.

4.9. Changes to Protocol-Planned Analyses

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

5. Sample Size Determination

Approximately 939 participants will be randomly assigned to LY3209590 and insulin degludec in a 2:1 ratio. With the assumption of 15% dropout at Week 26 (Visit 22), approximately 532 and 266 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 Week 26 (Visit 22) in HbA1c in participants with T2D currently on basal insulin.

Assuming a NIM of 0.4%, no true difference between treatment groups, and a SD of 1.1%, 798 completers (532 on LY3209590 and 266 on insulin degludec) will provide greater than 99% statistical power to show noninferiority between LY3209590 and insulin degludec using the upper limit of a 2-sided 95% confidence interval (LY3209590 – insulin degludec). This sample size also has at least 95% statistical power to show noninferiority between LY3209590 and insulin degludec using a 0.3% NIM at Week 26 (Visit 22).

The 798 completers will provide 95% statistical power to demonstrate the superiority (LY3209590 vs. insulin degludec) of change in HbA1c from baseline to 26 weeks (assuming a SD of 1.1% and true mean difference is -0.3%) using the alpha of 0.05.

The 798 completers will provide at least 95% statistical power to show the superiority of the percentage of time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive during the CGM session prior to Week 26 (Visit 22) between LY3209590 and insulin degludec (assuming a SD of 18% and true mean difference is 5%) at alpha = 0.05.

The 798 participants will provide at least 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 treatment phase up to Week 78 (assuming event rate of 0.67 [SD = 2.6] and 1.1 [SD = 2.6] events per participant per year for LY3209590 and insulin degludec, respectively) using a negative binomial distribution at alpha = 0.05.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Demographic and baseline characteristics including but not limited to age (years), age groups (<65, ≥65 and <75, ≥75 and <85, ≥85 years), sex, ethnicity, race, country, region, height, weight (kg), body mass index (BMI: kg/m^2), BMI groups (<25, ≥25 and <30, ≥30 and <35, ≥35 kg/m^2), eGFR groups (<30, ≥30 and <60, ≥60 and <90, ≥90 mL/min/1.73 m^2), 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, baseline non-insulin antihyperglycemic medications (type and number) will be summarized by treatment group using the mITT, Randomized Population (if different from the mITT) and mITT Population, excluding inadvertently enrolled participants.

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

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

Historical conditions are conditions that end prior to inform consent and preexisting conditions are conditions that are still ongoing at inform consent. The number and percentage of participants with historical conditions will be summarized by treatment group using MedDRA PT using the mITT, Randomized Population (if different from the mITT) and mITT Population, excluding inadvertently enrolled participants. Events will be ordered by decreasing frequency. 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 algorithm recommended dose based on the participant fasting blood glucose and hypoglycemia occurrence reported in e-diary. If the investigator does not agree with the algorithm recommended dose, the investigator will prescribe another dose for the participant and choose the reason of not following the algorithm recommended dose from a pre specified list of terms. The number and percentage of investigator prescribed doses different from algorithm recommended doses will be provided to evaluate the adherence to the algorithm dose. The reason for not following the algorithm recommended dose will also be summarized.

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

6.3. Appendix 3: Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

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

6.4. Appendix 4: Concomitant Therapy

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

The number and percentages of participants who take concomitant medication will be summarized by treatment using PTs nested within Anatomical Therapeutic Chemical (ATC) 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 patients' safety. The IPD category and details of IPD identification are provided in the trial issue management plan.

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

6.6. Appendix 6: Derivation of CGM Variables

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

- Two weeks in screening/lead-in period with the data download at Week 0 (Visit 3),
- Four weeks after the initiation of study treatment with the data download at Week 4 (Visit 7),
- Four weeks near the end of weekly titration period with the data download at Week 12 (Visit 15),
- Four weeks near the primary endpoint with the data download at Week 26 (Visit 22),
- Four weeks near the end of 1-year treatment with the data download at Week 52 (Visit 30),
- Four weeks near the end of study treatment period with the data download at Week 78 (Visit 37), and
- Four weeks after the end of study treatment period with the data download at Week 83 (Visit 802).

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

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

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

Glucose reading intervals >15 minutes will be treated as missing data and not be counted in the length of the analysis periods.

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

Period	Definition	Minimum Valid CGM Time Period for a Session
Valid CGM Day (00:00-23:59)	≥70% of expected values available (≥202 of 288 values)	≥ 3 valid CGM days within a visit defines a valid CGM visit. A valid CGM session only includes valid CGM visits.
Valid CGM Nighttime (00:00-05:59)	≥70% of expected values available (≥50 of 72 values)	≥ 3 valid CGM Nighttime periods within a visit defines a valid CGM visit. A valid CGM session for nighttime only includes valid CGM visits.
Valid CGM Daytime (06:00-23:59)	≥70% of expected values available 151 of 216 values)	≥ 3 valid CGM Daytime periods within a visit defines a valid CGM visit. A valid CGM session for daytime only includes valid CGM visits.

Abbreviation: CGM = continuous glucose monitoring.

For the primary analysis, CGM data must meet above criteria for the period in order to be included as a valid CGM period. Sensitivity analysis will be done for selected parameters 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 CGM session, based upon the observed CGM measures.

6.6.1. Glucose in Target Ranges, Hypoglycemia or Hyperglycemia

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

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

The percentage of time within a glucose range (target, hypoglycemia or hyperglycemia ranges) will be calculated as the number of observations within the specified range divided by the number of observations in the time interval (for example, 24-hour period). The average percentage of time among valid CGM days for the corresponding time interval during each CGM session will be used in the analysis.

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

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

- The percentage of time within a normal glycemia range (defined as between 70 mg/dL and 180 mg/dL [3.9 and 10.0 mmol/L] inclusive) >70%.

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

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

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

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

6.6.2. Hypoglycemic Episode

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

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	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 (as captured in continuous glucose monitor [CGM]).
Note: Starting time and ending time are regardless of number of BG readings.

If the truncated time interval is >7 and ≤15 minutes, linear interpolation will be used to impute the missing data at 5-minute intervals as described in Section 6.6.

If the truncated time interval is >15 minutes:

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

The average duration, incidence, event rate of the Level 1 or 2 and Level 2 hypoglycemia episodes will be analyzed for each CGM session 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 during the given CGM session by the number of episodes and used in the analysis. The hypoglycemia event rate (events/participant/year) will be calculated by dividing the number episodes by the number of valid CGM days × 365.25 days.

6.6.3. Mean Glucose and Glucose Management Indicator

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

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

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

6.6.4. Glycemic Variability

Glycemic variability will be derived using the notation below:

i represents a time point within a time period (a 24-hour period, daytime or nighttime)

n represents the number of time points within the time period

k represents a valid CGM day within a visit

m represents the number of valid CGM days in the specific time period at a visit

$BG_{k,i}$ represents the glucose value at time point *i* on day *k* unless otherwise specified.

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

6.6.4.1. Within-Day Variability

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

Within-day glucose SD (Rodbard 2009):

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

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

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

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 average across days within a CGM session. The calculations of LBGI, HBGI and BGRI take the following steps:

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

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

2. Compute BG risk for each reading

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

3. Compute LBGI and HBGI

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

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

4. Compute BGRI

$$\mathrm{BGRI} = \mathrm{LBGI} + \mathrm{HBGI}$$

6.6.4.2. Between-Day Variability

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

Between-day glucose SD (Rodbard 2009):

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

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

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

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.

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

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

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

- Amaurosis
- Amaurosis fugax
- Arteriosclerotic retinopathy
- Blindness
- Blindness transient
- Blindness unilateral
- Choroidal neovascularisation
- Cystoid macular oedema
- Detachment of macular retinal pigment epithelium
- Detachment of retinal pigment epithelium
- Diabetic blindness
- Diabetic eye disease
- Diabetic retinal oedema
- Diabetic retinopathy
- Diabetic uveitis
- Diplopia
- Exudative retinopathy
- Eye laser surgery
- Fundoscopy
- Fundoscopy abnormal
- Intra-ocular injection
- Macular detachment

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

6.8. Appendix 8: MedDRA PT for Peripheral Edema

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

- Acute pulmonary oedema
- Ascites
- Brain oedema
- Bronchial oedema
- Capillary leak syndrome
- Cerebral oedema management
- Compression garment application
- Cytotoxic oedema
- Effusion

- Fluid retention
- Gastrointestinal oedema
- Generalised oedema
- Gravitational oedema
- Hydraemia
- Hypervolaemia
- Hypoosmolar state
- Lipoedema
- Lymphoedema
- Negative pressure pulmonary oedema
- Non-cardiogenic pulmonary oedema
- Non-pitting oedema
- Oedema
- Oedema blister
- Oedema due to cardiac disease
- Oedema due to hepatic disease
- Oedema due to renal disease
- Oedema mucosal
- Oedema peripheral
- Pelvic fluid collection
- Pericardial effusion
- Perinephric collection
- Perinephric oedema
- Peripheral swelling
- Pleural effusion
- Pulmonary oedema
- Retroperitoneal effusion
- Retroperitoneal oedema
- Skin oedema
- Skin swelling
- Subdural effusion
- Swelling
- Visceral oedema

6.9. Appendix 9: Empirical Estimation of Relative Event Rate

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

Let X_{ij} denote the count response variable for patient j in treatment group i. Let $Y_i = \sum_j X_{ij}$ be the total number of events for treatment group i, and T_i denote the exposure for treatment group

i. Let *i* = 0 for the control group and *i* = 1 for the experimental treatment group. The event rate for treatment group *i* can be calculated as

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

The empirical variance of $\hat{r}_I$ is

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.10. Appendix 10: Definition for Persistent/Recurrent Hypoglycemia

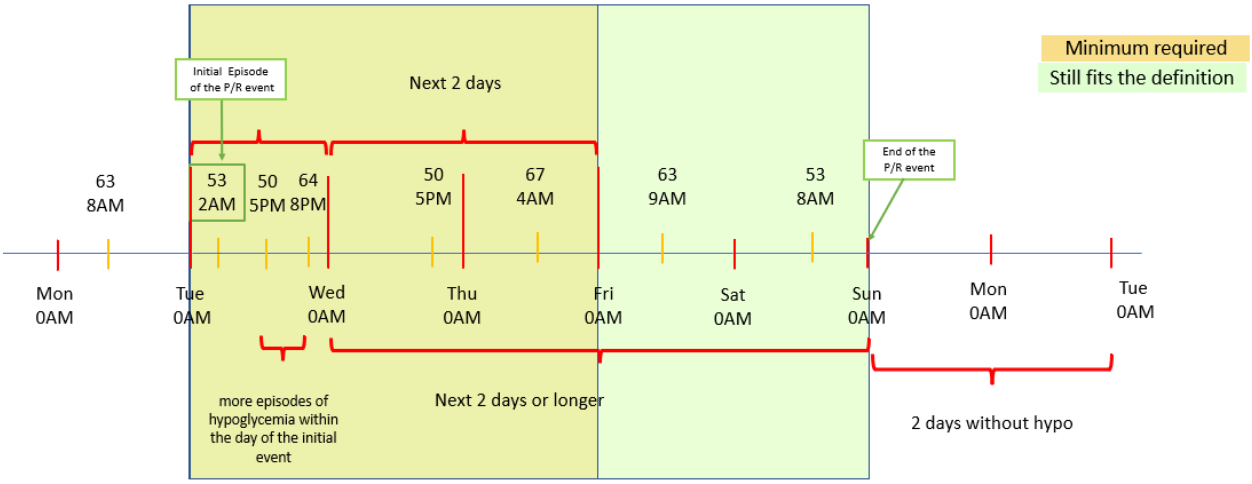
A P-R hypoglycemia based on programming search in the e-diary database for hypoglycemic events that meet prespecified criteria - is defined as a set of hypoglycemic episodes that:

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

AND

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

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



6.11. Appendix 11: Statistical Analysis for Japan

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

- Japanese population
- Japanese population whose prestudy basal insulin dose <10 U/day enrolled based on the I8H-MC-BDCU protocol addendum (2.1)
- Japanese population whose prestudy basal insulin dose ≥10 U/day

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

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.

6.12. Appendix 12: Abnormality Level Criteria for Chemistry and Hematology Laboratory Results

Parameter (in conventional unit)	High/Low	Level 1	Level 2	Level 3
General Chemistry				
Sodium (mEq/L)	Low	<132	<130	<125
	High	>150	>155	>160
Potassium (mEq/L)	Low	<3.6	<3.4	<3.0
	High	>5.5	>6	>6.5
Chloride (mEq/L)	Low	<95	<88	<80
	High	>108	>112	>115
Bicarbonate (mEq/L)	Low	<20	<18	<15
	High	NA	NA	>30
Blood urea nitrogen (mg/dL)	High	>23	>27	>31
Calcium (mg/dL)	Low	<8.4	<8.0	<7.5
	High	>10.5	>11.0	>12.0
Phosphate (mg/dL)	Low	<2.5	<2.0	<1.4
Protein (total) (g/dL)	Low	<6.0	<5.4	<5.0
Albumin (g/dL)	Low	<3.1	<2.5	<2.0
Uric Acid (urate) (mg/dL)	High	>7.0	NA	NA
Kidney Function				
Creatinine (mg/dL)	Increase	≥1.5 × baseline	≥2.0 × baseline	≥3.0 × baseline
eGFR (ml/min/1.73m2)	Decrease	≥25% decrease from baseline	≥50% decrease from baseline	≥75% decrease from baseline
Lipids				
Cholesterol (total) (mg/dL)	High	>200	>240	>300
HDL (mg/dL) in males	Low	<40	<30	<20
HDL (mg/dL) in females	Low	<50	<40	<20
LDL (mg/dL)	High	>130	>160	>190
Triglycerides (mg/dL)	High	>150	>300	>500
Hematology				
Complete Blood Count				
WBC (cells/µL)	Low	<3500	<3000	<1000
	High	>10,800	>13,000	>15,000
Hemoglobin (g/dL)	Decrease	NA	>1.5 decrease from baseline	>2 decrease from baseline
	Increase	NA	>2 increase from baseline	>3 increase from baseline
Platelets (cells/µL)	Low	<140,000	<125,000	<100,000
Hemoglobin, male (g/dL)	Low	12.5-13.5	<12.5	<10.5
Hemoglobin, female (g/dL)	Low	11.0 – 12.0	<11	<9.5
WBC Differential				
Lymphocytes (cells/µL)	Low	<1000	<750	<500
	High	>4000	>10000	>20000
Neutrophils (cells/µL)	Low	<2000	<1000	<500
Eosinophils (cells/µL)	High	>650	>1500	>5000
Coagulation Studies				
Prothrombin Time (seconds)	Increase	>1.1 × ULN	>1.3 × ULN	>1.5 × ULN

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

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

6.13. Appendix 13: 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 $Var\left(\hat{\boldsymbol{\theta}}\right) = diag\left(\left[se(\hat{\theta}_1)\right]^2, \left[se(\hat{\theta}_2)\right]^2, \ldots, \left[se(\hat{\theta}_k)\right]^2\right)$.

A chi-square test (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

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

Approved on 27 May 2024 GMT

7. References

Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593-1603. https://doi.org/10.2337/dci19-0028. Epub 2019 Jun 8.

Battelino T, Alexander C, Amiel S. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol.* 2023;11:42–57. https://doi.org/10.1016/ S2213-8587(22)00319-9

Bergenstal RM, Beck RW, Close KL, et al. Glucose management indicator (GMI): a new term for estimating A1c from continuous glucose monitoring. *Diabetes Care*. 2018;41(11):2275-2280. https://doi.org/10.2337/dc18-158

Bradley C. (ed). *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Chur, Switzerland: Harwood Academic Publishers; 1994. https://doi.org/10.1186/1477-7525-5-57

Bradley C. Diabetes treatment satisfaction questionnaire: change version for use alongside status version provides appropriate solution where ceiling effects occur. *Diabetes Care*. 1999;22(3):530-532. https://doi.org/10.2337/diacare.22.3.530

Bradley C, Lewis KS. Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. *Diabet Med*. 1990;7(5):445-451. https://doi.org/10.1111/j.1464-5491.1990.tb01421.x

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med.* 2009;28(4):586-604. https://doi.org/10.1002/sim.3495

Bretz F, Posch M, Glimm E, et al. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J.* 2011;53(6):894-913. https://doi.org/10.1002/bimj.201000239

Brod M, Hammer M, Christensen T, et al. Understanding and assessing the impact of treatment in diabetes: the Treatment-Related Impact Measures for Diabetes and Devices (TRIM-Diabetes and TRIM-Diabetes Device). *Health Qual Life Outcomes*. 2009;7:83. https://doi.org/10.1186/1477-7525-7-83

Clarke W, Kovatchev B. Statistical tools to analyze continuous glucose monitor data. *Diabetes Technol Ther*. 2009;11(Suppl 1):S45-S54. https://doi.org/10.1089/dia.2008.0138

[EuroQol] European Quality of Life Research Foundation. EQ-5D-5L user guide, version 3.0. Updated September 2019. Available at: https://euroqol.org/publications/user-guides

[FDA] Food and Drug Administration. Standard safety tables and figures: integrated guide, 2022. Available at: https://downloads.regulations.gov/FDA-2022-N-1961-0046/attachment_1.pdf

Kovatchev BP, Otto E, Cox D, et al. Evaluation of a new measure of blood glucose variability in diabetes. *Diabetes Care*. 2006;29(11):2433–2438. https://doi.org/10.2337/dc06-1085

Kovatchev BP, Shields D, Breton M. Graphical and numerical evaluation of continuous glucose sensing time lag. *Diabetes Technol Ther*. 2009;11(3):139-143. https://doi.org/10.1089/dia.2008.0044

Nelson WB. *Recurrent Events Analysis for Product Repairs, Disease Recurrences, and Other Applications, The ASA-SIAM Series on Statistics and Applied Probability*. Philadelphia, PA: Society for Industrial and Applied Mathematics; 2003.

[PHUSE] Pharmaceutical Users Software Exchange. Analyses and displays associated with laboratory analyte measurements in Phase 2-4 clinical trials and integrated submission documents – update to recommendations. 2022. Available at: https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Safety+Analytics/WP068.pdf

Qu Y, Dai B. Return-to-baseline multiple imputation for missing values in clinical trials. *Pharm Stat.* 2022;21(3):641-653. https://doi.org/10.1002/pst.2191

Qu Y, Luo J. Estimation of group means when adjusting for covariates in generalized linear models. *Pharm Stat*. 2015;14(1):56-62. https://doi.org/10.1002/pst.1658

Rodbard D. New and improved methods to characterize glycemic variability using continuous glucose monitoring. *Diabetes Technol Ther*. 2009;11(9):551-565. https://doi.org/10.1089/dia.2009.0015

Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Hoboken, NJ: John Wiley & Sons, Inc; 1987.

Ye T, Bannick M, Yi Y, Shao J. Robust variance estimation for covariate-adjusted unconditional treatment effect in randomized clinical trials with binary outcomes. *Stat Theory Relat Fields.* 2023;7(2):159-163. https://doi.org/10.1080/24754269.2023.2205802

Signature Page for VV-CLIN-122290 v2.0

Approval	PPD 27-May-2024 09:34:48 GMT+0000

Signature Page for VV-CLIN-122290 v2.0

Approved on 27 May 2024 GMT