Statistical Analysis Plan: I8H-MC-BDCL (Version 2)

A Phase 2, Randomized, Parallel, Open-Label Comparator-Controlled Trial to Evaluate the Safety and Efficacy of LY3209590 in Insulin-Naïve Patients with Type 2 Diabetes Mellitus

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1. Statistical Analysis Plan for Protocol I8H-MC-BDCL: A Phase 2, Randomized, Parallel, Open-Label Comparator-Controlled Trial to Evaluate the Safety and Efficacy of LY3209590 in Insulin-Naïve Patients with Type 2 Diabetes Mellitus

Basal Insulin-Fc (LY3209590) Diabetes Mellitus

This is a Phase 2, open-label, multicenter, multinational, randomized, controlled, parallel-design trial comparing LY3209590 to insulin Degludec in insulin-naïve patients with type 2 diabetes mellitus treated with a stable dose of metformin for at least 3 months prior to screening.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I8H-MC-BDCL
Phase 2

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

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on 26 June 2020, prior to the first patient visit of the study. The SAP Version 1 was based on the Protocol I8H-MC-BDCL, the amendment Protocol I8H-MC-BDCL(a) and the amendment Protocol I8H-MC-BDCL(b); approved on 11 December 2019, 08 April 2020, and 12 June 2020, respectively.

This SAP is the second version based on the amendment Protocol I8H-MC-BDCL(c) and the amendment Protocol I8H-MC-BDCL(d), approved on 14 August 2020 and 28 October 2020 respectively, in addition to the above protocol and protocol amendments. This SAP is approved prior to the last patient visit. The main changes are summarized as following:

- Updating the analyses based on the removal of LY3209590 Algorithm 2 to align with the amendment Protocol I8H-MC-BDCL(d)
- Replacing the 2-step imputation method with return to baseline imputation for the supportive estimand
- Replacing the longitudinal logistic regression with logistic regression based on multiple imputation for the HbA1c target analyses
- Adding potential sensitivity analysis which will censor the data from patients who significantly deviated from the study dose algorithm
- Adding sensitivity analysis for the comparison between pooled LY3209590 group and insulin degludec
- Deleting the t-test for exposure comparison
- Adding the adjudication details for nonfatal cardiovascular events
- Adding details for analyses (for example, analysis models for different types of flash glucose monitoring [FGM]-derived variables, analysis population)
- Clarifying that the study team is unblinded to the study treatment for patient safety monitoring
- Updating the analyses for hypoglycemia event rates from negative binomial regression to empirical method
- Adding one more subgroup for analyses: Concomitant medication (metformin alone and metformin in combination with other allowed oral antidiabetic medications)
- Updating the subgroup analyses for documented, nocturnal, and non-nocturnal hypoglycemia rates (defined by glucose <70 mg/dL [3.9 mmol/L] and glucose ≥54 mg/dL [3.0 mmol/L]) during 0-26 weeks.

4. Study Objectives

4.1. Primary Objective

To investigate the effect of LY3209590 compared with insulin degludec in hemoglobin A1c (HbA1c) change from baseline to Week 26 among insulin-naïve patients with type 2 diabetes mellitus (T2DM).

4.2. Secondary Objectives

4.2.1. Efficacy

To investigate the efficacy of LY3209590 compared with insulin degludec for the following endpoints:

1. HbA1c change from baseline to Week 12;
2. Fasting glucose change from baseline to Weeks 12 and 26.

4.2.2. Safety

To investigate the safety of LY3209590 compared with insulin degludec for the following endpoints:

1. Incidence and rate of hypoglycemia events during the treatment period;
2. Incidence of treatment-emergent serious adverse events (TE-SAEs).

4.3. Exploratory Objectives

To investigate other safety and efficacy measures for LY3209590 for the following endpoints:

1. Insulin dose at baseline and Week 26;
2. Treatment-emergent adverse events (TEAEs);
3. Incidence and rate of hypoglycemia events during the post-treatment follow-up period;
4. Discontinuation of investigational product (IP) due to adverse events (AEs);
5. Clinical laboratory results;
6. Injection site reactions;
7. Liver aminotransferase change from baseline to Weeks 12 and 26;
8. Triglyceride and FFA change from baseline to Weeks 12 and 26;
9. Body weight change from baseline at Weeks 12 and 26;
10. Glucose time in target range, time in hyperglycemia, time in hypoglycemia using FGM
11. Lipids (cholesterol, LDL, HDL, triglycerides);
12. Six-point self-monitoring of blood glucose (SMBG) profiles;

13. The frequency of antibody formation to LY3209590;
14. Incidence and percentage of missed doses of LY3209590 and insulin degludec.

5. A Priori Statistical Methods

5.1. General Considerations

All data will be entered, verified, and archived at a contract research organization (CRO) external to Eli Lilly and Company (Lilly) and/or at Lilly. Data listings, summaries, and analyses will be performed by a CRO and/or by Lilly under the guidance and approval of statisticians at Lilly.

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

The following populations are defined for purpose of analysis:

Population	Description
Entered/Enrolled Population	All participants who sign the ICF
Randomized Population	All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. The participants previously randomized to LY3209590 Algorithm 2 will be pooled with the participants randomized to Algorithm 1 and all of these participants will be analyzed as one treatment group of LY3209590.
Efficacy Population	All participants randomized to either LY3209590 Algorithm 1 or insulin degludec and took at least 1 dose of study treatment. Participants will be analyzed according to the treatment they were assigned.
Safety Population	All participants randomly assigned to study treatment and who took at least 1 dose of study treatment. The participants previously randomized to LY3209590 Algorithm 2 will be pooled with the participants randomized to Algorithm 1 and all of these participants will be analyzed as one treatment group of LY3209590.
Pharmacokinetic Population	All randomized participants who received at least 1 dose of LY3209590 and have at least 1 evaluable PK sample.

Abbreviations: ICF = informed consent form; PK = pharmacokinetics.

Unless otherwise stated, the efficacy analyses will be conducted on efficacy analyses set (EAS) based on Efficacy Population using the data up to the study treatment discontinuation (defined as

the observed data with collection date before or on the last dose date +10 days). Sensitivity analyses for selected efficacy measures may be conducted on the Randomized Population using the data up to the study treatment discontinuation.

Unless otherwise stated, the safety analyses will be conducted on the safety analyses set based on the Safety Population using all data collected during the study including treatment and follow-up periods regardless of the treatment disposition status. The safety measures will be summarized and compared between LY3209590 (by pooling LY3209590 Algorithm 1 and LY3209590 Algorithm 2 data) and insulin degludec. Safety parameters derived from FGM measures will be summarized and compared between LY3209590 Algorithm 1 and insulin degludec.

Unless otherwise specified, the baseline value used for the analyses will be the last non-missing value obtained for each participant prior to or on the date of first study IP dose (or randomization visit date if first dose date is missing). The baseline liver enzyme lab measures will be the average of all assessments prior to and at randomization visit.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, unless otherwise stated, and all confidence intervals (CIs) will be given at a 2-sided 90% level.

Puerto Rico and the United States (US) are always pooled in the analysis, as Puerto Rico will be considered part of US during randomization. All analyses using country in the model will use pooled country, unless otherwise specified. No other pooling of countries is needed.

For continuous measurements, summary statistics will include sample size, mean, median, standard deviation (SD), minimum, and maximum. For certain variables that are considered to be log-normally distributed, the geometric mean and coefficient of variation (CV) will be provided instead.

For categorical measurements, summary statistics will include sample size, frequency, and percentage. Fisher's exact test will be used. Chi-squared test will be used for multi-category variables.

A mixed-model repeated measures (MMRM) model will be used for continuous outcomes with repeated postbaseline measurements to compare treatment arms, unless otherwise noted. Treatment comparisons will be performed by the treatment difference in least-squares means (LS mean). Means and LS mean by treatment group and visit, along with the standard error of LS mean, 90% CIs of the treatment differences along with the p-value for the treatment comparison will be displayed. For the change from baseline, p-value for the within-treatment comparison will also be displayed. For selected parameters, log-transformed values will be analyzed in the MMRM model instead. The actual, change from baseline and percentage change from baseline will be presented using the derivation based on the output from the MMRM model.

In this study, the negative binomial regression will estimate Group Mean instead of LS mean and use delta method 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.

Sensitivity analyses may be conducted for selected safety and efficacy measures by excluding data from patients who significantly deviated from the study dose algorithm, for example, patients who received repeated loading doses. The study team will review patient study dose data and identify the patients who will be excluded from the sensitivity analyses prior to the final lock of the study data.

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

5.2. Patient Disposition

All randomized participants who discontinue the study/treatment will be identified, and a reason for their discontinuation will be given. The reasons for study/treatment discontinuations will be summarized by treatment using the Randomized Population and the Efficacy Population. Comparisons will be conducted using the Fisher's exact test. A listing of the primary reasons for study/treatment discontinuations will be generated for the Enrolled Population.

Reasons for discontinuation prior to randomization will also be summarized. A listing of the randomized treatments for this study will be provided.

5.3. Patient Characteristics

Demographic and baseline characteristics including but not limited to age (years), age groups (<65 years, ≥65 years and <75 years, ≥75 years), sex, ethnicity, race, country, region, weight (kg), body mass index (BMI: kg/m^2), BMI groups (<25, ≥25 and <30, ≥30 and <35, and ≥35 kg/m^2), eGFR groups (estimated glomerular filtration rate based on the modified Modification of Diet in Renal Disease [MDRD] equation: ≥90, <90 and ≥60, <60 and ≥30, and <30 mL/min/1.73 m^2), duration of diabetes (years), baseline substance use (alcohol, drug, tobacco and caffeine baseline use status), baseline systolic blood pressure, baseline diastolic blood pressure, baseline HbA1c (% and mmol/mol), baseline HbA1c groups (<8.5%, ≥8.5%), fasting serum glucose (FSG: mmol/L and mg/dL), HbA1c screening group (HbA1c, <8.5% and ≥8.5% at Visit 1), DPPIV use, SGLT2 use and combination of OAM use will be summarized by treatment group for the Randomized Population, the Efficacy Population, and the Safety Population. Comparisons of categorical variables between treatment groups will be assessed using a Pearson Chi-Square test. Comparisons of continuous variables between the treatment groups will be performed using a 1-way analysis of variance with treatment as the fixed effect. The by-patient listing of demographic and selected baseline characteristics will be provided for all randomized patients.

Number of randomized patients and number of randomized patients discontinued per investigator within country for each treatment group will be summarized. In addition, number of enrolled patients per investigator within each country will also be summarized.

5.4. Concomitant Medications

Concomitant medications used during the treatment period will be summarized by treatment groups and will be compared between treatment groups using Fisher's exact test for the Safety Population. The percentages of patients who took concomitant medication will be summarized by treatment using Preferred Terms (PTs) nested within Anatomical Therapeutic Chemical (ATC) Level 3 codes. The concomitant medications will be ordered by decreasing frequency within each ATC level.

5.5. Treatment Adherence

Treatment adherence will be summarized using the EAS. For a given study participant, overall adherence for treatment period is based on the ratio of the total number of doses taken to the total number of required doses. CCI

[redacted]

Adherence to the dosing algorithm is required from Visit 3 (Randomization) up to Visit 20. The number and percentage of investigator prescribed doses that did not follow the algorithm recommended dose and the number and percentage of patient actual administration dose that did not follow the investigator prescribed dose will be provided.

Similar descriptive statistics will be provided for patients randomized to LY3209590 Algorithm 2 arm and took at least 1 study dose.

5.6. Protocol Deviations

Important protocol deviations (IPDs) defined as deviations from the study protocol that may compromise the data integrity and patients' safety will be summarized by treatment group for the Randomized Population and the Efficacy Population. The listing of IPDs for the Randomized Population will also be provided.

5.7. Primary Outcome and Methodology

The primary objective is to compare the HbA1c change from baseline to Week 26 between LY3209590 and insulin degludec and will be based on the primary estimand described below.

The primary estimand is the treatment differences in the change in HbA1c from baseline to 26 weeks for the targeted study population if all patients would adhere to the treatment without intercurrent events. The analysis data will include data up to the discontinuation of study treatment for the Efficacy Population with baseline and at least one non-missing postbaseline measurement. There may be missing values due to the early discontinuation of study treatment. The MMRM model will be used with the HbA1c changes at Week 6, 12, 16 and 26 (the primary endpoint) and the missing values will be imputed implicitly in the MMRM analysis under the assumption of missing at random. The MMRM model will include treatment (LY3209590 Algorithm 1, insulin degludec), strata (country, DPPIV [yes/no], SGLT2 [yes/no] and baseline BMI [<30, ≥ 30]), visit, and treatment by visit interaction and the baseline value of the dependent

variable as the fixed effects. The HbA1c is reported in unit of % 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). HbA1c analysis will be conducted based on both units.

In the MMRM model, the within-patient errors are modeled as an unstructured variance-covariance matrix. If the analysis fails to converge, the following variance-covariance matrix 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

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for the MMRM models. The following is an example SAS code:

```
proc mixed data=DATA;
       class TREATMENT STRATIFICATIONS VISIT PATIENT;
       model HbA1c=BASELINE TREATMENT STRATIFICATIONS VISIT
                   VISIT*TREATMENT / solution ddfm=kr;
       repeated VISIT / subject=PATIENT type=un;
       lsmeans TREATMENT*VISIT/ pdiff cl alpha=0.1 om=DATA;
run;
```

The 2-sided 90% CI of the LS mean for individual treatment groups, treatment LS mean difference (LY3209590 Algorithm 1 versus insulin degludec) in the HbA1c change from baseline to Week 26 will be estimated. Similar analysis based on the above MMRM model will also be provided for the comparison between LY3209590 (by pooling LY3209590 Algorithm 1 and LY3209590 Algorithm 2) and insulin degludec.

With the primary estimand, LY3209590 Algorithm 1 will be declared noninferior to insulin degludec if the upper limit of the 2-sided 90% CI for the LS mean difference in the HbA1c change from baseline is below +0.4%.

A supportive estimand is the treatment differences in HbA1c change from baseline to Week 26 for the targeted study population regardless of the use of rescue medication or taking study medication. The analysis data will include all available data at Week 26 regardless of treatment disposition status for all randomized patients who took at least one dose of study treatment and have non-missing baseline. There will be missing endpoint due to early study discontinuation. The missing endpoint will be imputed by "return to baseline" imputation. Multiple imputations will be conducted and an analysis of covariance model including factors of treatment, country, DPPIV [yes/no], SGLT2 [yes/no], baseline BMI [<30, ≥30], and baseline HbA1c as covariates will be performed by imputation data set. Then, the inference will be based on the bootstrap method.

5.8. Secondary and Additional Efficacy Analyses

The primary population for the secondary analysis on HbA1c reduction is the EAS. Treatment comparison at 26 weeks will be used to assess the differences. The 2-sided 90% CI for the LS mean of the differences in the change in HbA1c at 26 weeks will also be constructed.

The following secondary efficacy outcomes will be analyzed based on the EAS using the same MMRM model as the primary analysis with the addition term of HbA1c strata (<8.5% and ≥8.5%) for non-HbA1c measures:

1. HbA1c change from baseline to Week 12.
2. Fasting blood glucose (FBG) and change by SMBG from baseline to Week 12 and Week 26;
3. Fasting serum glucose (FSG) by laboratory and change from baseline at Weeks 12 and 26;
4. Between-day glucose variability measured by the SD and the CV of the FBG at Week 12 and 26;
5. Six-point SMBG profile (pre-meal and 2-hour postprandial SMBG measurements for the morning, midday, and evening meals) at Weeks 12 and 26.
6. Within-day and between-day glucose variability measured by the SD and the CV of 6-point SMBG.

For the between-day and within-day glucose variability, the variables will take a log-transformation before performing the MMRM analysis.

The proportion of the patients with HbA1c <7.0% (or ≤6.5%) will be analyzed based on the multiple imputation with the following steps: 1) imputing the missing values in the continuous HbA1c by treatment, 2) dichotomizing the "complete" continuous HbA1c into binary based on the threshold, then 3) fitting the logistic regression model at each scheduled postbaseline visit, and 4) using Rubin's rule to combine the results. In the logistic regression model, the independent variables of treatment, country, BMI strata (BMI <30 or ≥30), DPPIV use [yes/no], SGLT2 use [yes/no], baseline HbA1c value will be used.

The above analyses may be repeated to compare LY3209590 (by pooling LY3209590 Algorithm 1 and LY3209590 Algorithm 2) with insulin degludec.

The insulin dose units are different between LY3209590 (mg) and insulin degludec (unit). Therefore, descriptive statistics will be provided for the insulin dose and the dose change from baseline. A loading dose strategy was used only for the first dose of LY3209590. One third of the loading dose will be used as the baseline dose of LY3209590 in the analysis while the dose of insulin degludec at Week 0 will be used as the baseline dose of insulin degludec. No treatment comparison will be conducted. Two sample t-test will be conducted to assess the change from baseline within treatment group.

5.9. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamics (PK/PD) analyses will be conducted by PK/PD group.

5.10. Safety Analyses

Safety measures will include AEs, vital signs, hypoglycemic episodes, treatment exposure, adjudicated cardiovascular events, laboratory measurements, electrocardiograms (ECGs) and immunogenicity. Safety analysis will be reported for the Safety Population using data measured while on treatment and after study drug discontinuation. Unless otherwise specified, the comparison will be between LY3209590 (by pooling LY3209590 Algorithm 1 and LY3209590 Algorithm 2) and insulin degludec.

5.10.1. Study Drug Exposure

Exposure in days in the study will be calculated for each patient and summarized by treatment group. Exposure during the treatment period will be calculated from date of first study basal insulin dose collected in the electronic case report form (eCRF) to date of discontinuation from study treatment (i.e., the last dose date for insulin degludec, and the last dose date + 7 days for LY3209590). The sum of exposure in total patient years will also be provided.

Frequency of subjects falling into the following different exposure ranges will also be summarized: >0 days, ≥7 days, ≥14 days, ≥30 days (1 month), ≥60 days (2 months), ≥90 days (3 months), ≥120 days (4 months), ≥183 days (6 months) days.

In addition, the duration of follow-up in days for each individual patient is calculated from the date of last dose of study drug for insulin degludec or the date of last dose of study drug + 7 days for LY3209590 to the last study visit date. The duration of the follow-up in days will be summarized (n, mean, standard deviation, minimum, maximum, median, and sum in total patient years) by treatment group.

The duration on study from date of the first study drug to the last study visit date (including the follow-up visit) will also be summarized by treatment group, the following summary statistics will be provided: n, mean, standard deviation, minimum, maximum, median, and sum in total patient years.

A by-patient listing of drug exposure data will be created to provide data for the CSR.

5.10.2. Adverse Events

Adverse events will be summarized as TEAEs (defined as events that are newly reported after the first dose of study basal insulin or reported to worsen in severity from baseline) and compared between treatments unless otherwise specified. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) will be used in determining the treatment-emergent status. The maximum severity for each LLT during the baseline period will be used as baseline severity. All analysis will be performed on the data collected from the date of first dose of study drug (or the randomization visit date if date of first dose is not available) to the end of the study (up to Visit 801).

The incidence of patients with at least 1 TEAE and the incidence of TEAEs by PT and system organ class (SOC) will be presented by treatment group. The number and percentage of patients with TEAEs will be summarized by treatment using MedDRA PTs nested within SOC. Events will be ordered by decreasing frequency within SOC.

The number and percentages of patients with TEAEs (≥2% before rounding) will be summarized by treatment using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency.

The incidence of participants with at least 1 TEAE assessed as possibly related to the IP will be summarized by treatment group using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. In addition, a summary of TEAEs by maximum severity will be presented descriptively by treatment group.

Discontinuations due to AEs will be summarized by PT and compared between treatment groups using Fisher's exact test for the Safety Population.

All SAEs (including death) will be listed by patient for the Safety Population.

Summary of TE-SAEs similar to summaries for the proportion of patients experiencing each reported TEAE by SOC will be included for the Safety Population.

5.10.3. Adverse Events of Special Interest (AESI)

Summary and analysis of TEAEs related to the following adverse events of special interest (AESIs) is specified in this section:

- deaths and nonfatal cardiovascular events
- hypoglycemia events
- hepatobiliary events
- injection site reactions
- systematic hypersensitivity reactions

5.10.3.1. Death and Nonfatal Cardiovascular Events

Deaths and nonfatal cardiovascular AEs will be adjudicated by an independent Clinical Endpoint Committee with cardiology expertise. The following events will be adjudicated and listed by patient for the Safety Population: death due to cardiovascular events, myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack. The actual term and PT of the event, date of first dose and last dose of study drug, result of adjudication, and time from first dose to event will be listed.

5.10.3.2. Hypoglycemia Events

According to the 2020 American Diabetes Association standard of medical care in diabetes, there are two levels of hypoglycemia defined by glucose concentration:

- Level 1: glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
- Level 2: glucose <54 mg/dL (3.0 mmol/L)

With the above glucose reading requirement for Level 1 and 2 hypoglycemia, the following type of hypoglycemia events will be derived: documented hypoglycemia, documented nocturnal hypoglycemia (occurs between bedtime and waking), and documented non-nocturnal hypoglycemia (occurs between waking and bedtime).

Per the study protocol, severe hypoglycemia is reported as a serious AE. Severe hypoglycemia is defined in the protocol and is consistent with the ADA definition, but also requires investigator confirmation of neurological impairment. The 2020 American Diabetes Association standard of medical care in diabetes also classified severe hypoglycemia as Level 3 hypoglycemia. During a severe hypoglycemia episode, the participant has an altered mental status and cannot assist in his/her own care, may be semiconscious or unconscious, or experience coma with or without seizures, and may require assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This information will be collected in the patient eDiary and the severe hypoglycemia will be listed.

Table BDCL.1 provides the summary of statistical method for hypoglycemia event related analysis. Additionally, severe hypoglycemia events will be listed. The severe hypoglycemia reported as spontaneous AE in the eCRF will also be summarized by MedDRA PT. The Level 2 and Level 3 are usually 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.

Table BDCL.1. Hypoglycemia Event Related Analyses

Endpoint	Time Point*	Statistical Method
Rate of hypoglycemia events for Level 1 and Level 2/3 • Documented • Nocturnal • Non-Nocturnal	0-12, 0-26, 12-26 weeks, post-treatment period (up to Visit 801)*	Exposure-adjusted rate per year / 100 years (calculated by total number of events divided by total exposure for individual patients) will be provided and the empirical method (see Appendix 1 for details) will be used for treatment comparison.
Incidence of hypoglycemia events for Level 1 and Level 2/3 • Documented • Nocturnal • Non-Nocturnal	0-12, 0-26, 12-26 weeks, post-treatment period (up to Visit 801)*	Logistic regression will include treatment, baseline HbA1c in the model. Note that the logistic regression will be conducted when ≥10 patients with this event.
• Proportion of patients with HbA1c <7% without documented nocturnal hypoglycemia event (Level 1 and Level 2) • Proportion of patients with HbA1c ≤6.5% without documented nocturnal hypoglycemia event (Level 1 and Level 2)	0-26 weeks	Logistic regression will include treatment, country, DPPIV [yes/no], SGLT2 [yes/no], baseline BMI [<30, ≥30], and baseline HbA1c in the model.

Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; Level 2/3= Level 2 and Level 3 composite.

Note: The hypoglycemia rate per year during defined period is calculated by the number of hypoglycemia within the period/number of days patient at risk within the period*365.25 days. The hypoglycemia incidence during defined period indicates if the patient has at least 1 hypoglycemia events within the period (Yes/No). The baseline hypoglycemia rate is the rate calculated between Visit 2 and Visit 3.

*Analyses for endpoint during post-treatment period (up to Visit 801) will include all of the data after study drug discontinued on Safety population; analyses for endpoints during other time points will include all data before study drug discontinued on Safety population.

5.10.3.3. Hepatobiliary Events

The percentages of patients with treatment-emergent hepatic AEs will be summarized by treatment group using MedDRA PT nested within each SMQ ordered by decreasing frequency. The following SMQs based on MedDRA will be used to identify hepatic events:

- 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)

5.10.3.4. Injection Site Reactions

Injection site reactions will be evaluated using the spontaneous AE reporting of injection site reactions by the selected MedDRA PTs for the LY3209590 study program.

Table BDCL.2 contains a list of MedDRA PTs based on MedDRA (both narrow and broad scope) that will be used to identify potential injection site reaction from the spontaneous reported AEs.

The number and percentage of patients experiencing treatment-emergent potential injection site reaction identified using broad and narrow search strategy will be summarized and compared by treatment group using Fisher's exact test. The number and percentage of patients experiencing treatment-emergent potential injection site reactions that is judged to be related to study drug by the investigator will also be summarized and compared.

Table BDCL.2. List of MedDRA Preferred Terms (PTs) to Search for Injection Site Reaction Adverse Events (AEs)

Preferred Term	Preferred Term Code	Scope
Injection site abscess	10022044	Narrow
Injection site abscess sterile	10022045	Narrow
Injection site atrophy	10022048	Narrow
Injection site erythema	10022061	Narrow
Injection site hypertrophy	10022072	Narrow
Injection site induration	10022075	Narrow
Injection site infection	10022076	Narrow
Injection site inflammation	10022078	Narrow
Injection site irritation	10022079	Narrow
Injection site mass	10022081	Narrow
Injection site edema	10022085	Narrow
Injection site pruritus	10022093	Narrow
Injection site rash	10022094	Narrow
Injection site reaction	10022095	Narrow
Injection site warmth	10022112	Narrow
Injection site cellulitis	10050057	Narrow
Injection site swelling	10053425	Narrow
Injection site discomfort	10054266	Narrow
Injection site nodule	10057880	Narrow
Lipoatrophy	10024604	Narrow
Lipodystrophy acquired	10049287	Narrow
Partial lipodystrophy	10053857	Narrow
Lipohypertrophy	10062315	Narrow

Preferred Term	Preferred Term Code	Scope
Injection site bruising	10022052	Broad
Injection site haematoma	10022066	Broad
Injection site haemorrhage	10022067	Broad
Injection site pain	10022086	Broad

5.10.3.5. Systemic Hypersensitivity Reaction

The number and proportion of patients experiencing potential treatment-emergent systemic hypersensitivity reactions will be summarized and compared by treatment group using Fisher's exact test. The following MedDRA Standardized MedDRA Query (SMQ) will be used to identify potential systemic hypersensitivity reactions from all TEAEs:

- Anaphylactic reaction (SMQ). Besides using the narrow and broad terms designated within the SMQ, the following search algorithm will also be implemented as another approach to determine if a patient had an anaphylactic reaction: if a patient (had at least 1 event in Category A) or (had at least 1 event that is in Category B and also had at least 1 event that is in Category C) or (had at least 1 event that is in Category D and [also had at least 1 event in Category B or at least 1 event in Category C])
- Angioedema (SMQ)
- Hypersensitivity (SMQ)

Specifically, need to perform the following: (1) any narrow or algorithmic term from any 1 of the 3 SMQs indicated above (i.e., combined search across narrow and algorithmic portions of all 3 SMQs); (2) any narrow scope term within each SMQ, separately (i.e., narrow SMQ search); (3) any term within each SMQ, separately (i.e., broad SMQ search); (4) narrow scope term search within each SMQ, report the PT nested within each SMQ.

Note that an individual patient may contribute multiple events. Also, a single event may satisfy multiple SMQs, in which case the event contributes to every applicable SMQ.

5.10.4. Vital Signs and Body Weight

Vital signs and weight will be summarized by treatment group and visit. Change from baseline (last nonmissing value up to Visit 3) to postbaseline value for vital signs and weight will be summarized by treatment group and visit for patients who have both a baseline and at least 1 postbaseline result.

Treatment differences in mean change will be assessed using MMRM. The MMRM model will be used for the analysis during the treatment period and will contain the terms for treatment, baseline value, visit, and visit-by-treatment interaction as factors; patient as random effect; and CS as the variance-covariance structure. Only scheduled measures will be included in the MMRM analyses.

An analysis of covariance (ANCOVA) will also be conducted for the last nonmissing values during the study including the safety follow-up visit for the Safety Population. The ANCOVA model will use treatment, baseline value of the dependent variable as covariates.

The percentages of patients with treatment-emergent high or low vital signs at any time after randomization will be summarized and compared between treatment groups using Fisher's exact test. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit (140 mm Hg for systolic blood pressure, 90 mm Hg for diastolic blood pressure, and 100 bpm for pulse) at baseline to a value greater than the high limit at any time that meets the specified change criteria after randomization. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit (90 mm Hg for systolic blood pressure, 50 mm Hg for diastolic blood pressure, and 50 bpm for pulse) at baseline to a value less than the low limit at any time that meets the specified change criteria after randomization. Patients with missing baseline measures will be excluded from this analysis unless otherwise specified. Scheduled visits, unscheduled visits, and retest measurements will be included in this analysis. Table BDCL.3 will be used to define the low and high limits and change thresholds.

Table BDCL.3. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15

Abbreviations: BP = blood pressure; bpm = beats per minute; mm Hg = millimeters of mercury.

5.10.5. Laboratory Measures

The data from laboratory testing will be summarized by treatment group and visit. Change from baseline (last nonmissing value up to Visit 3) to postbaseline value for laboratory tests (except for FSG, HbA1c, and Antibody) will be summarized for patients who have both a baseline and at least 1 postbaseline result. Treatment differences in mean change for these laboratory tests will be evaluated using MMRM model. The MMRM model will be used for the analysis during the treatment period and will contain the term for treatment, baseline value, visit, and visit-by-treatment interaction as factors, patient as random effect, and compound symmetric as the variance-covariance structure. Analyses will be provided in both international units (SI) and conventional units (CN). The MMRM analysis will only include lab tests for the scheduled visits specified in the protocol. For some selected laboratory measures, log-transformed value will be used in MMRM when necessary, and the geometric LS means as well as the percentage change from baseline will be reported.

The last nonmissing values during the study including the safety follow-up visit for the Safety Population will also be analyzed by an ANCOVA model. The ANCOVA model will use treatment, baseline value of the dependent variable as covariates. For some selected laboratory measures, log-transformed value will be used in the ANCOVA model.

The percentages of patients with treatment-emergent abnormal laboratory results at any time after randomization (including the treatment period and follow-up period) will be summarized

and compared between treatment groups using Fisher's exact test. A treatment-emergent abnormal result is defined as a change from normal at baseline to abnormal at any time after randomization. Covance reference ranges will generally be used to define the low and high limits. Patients with missing baseline lab measures will be excluded from this analysis unless otherwise specified. Scheduled visits, unscheduled visits, and retest measurements will be included in this analysis.

A lab listing in the Safety Population who had an treatment-emergent abnormal laboratory value during the study will be provided, including the actual measurement, abnormal result, and reference low or high limits.

5.10.5.1. Lipid Measures

Triglycerides, total cholesterol, LDL-C, and HDL-C (results from fasting samples) will take log-transformation before being analyzed by MMRM model defined above for the Safety Population. The last nonmissing measurements will also be log-transformed and analyzed by the previously defined ANCOVA model.

A listing of patients with postbaseline fasting triglyceride value ≥400 mg/dL or non-fasting triglycerides >600 will be provided (scheduled visits, unscheduled visits, and repeat measurements will be included).

5.10.5.2. Liver Enzyme Elevation Measures

The liver enzymes and biomarkers (alanine aminotransferase [ALT], aspartate aminotransferase [AST], Alkaline phosphatase [ALP], total bilirubin [TBL] and Gamma glutamyl transferase [GGT]) will take log-transformation before performing the MMRM and ANCOVA analyses. In addition, the percentage of patients with the following elevations in liver enzymes at any postbaseline visit after randomization including the treatment period and post-treatment follow-up period will be summarized for subsets based on baseline categories.

- The analysis of any postbaseline ALT (AST) ≥3 fold (3X) ULN will contain 4 baseline subsets:
    - patients whose non-missing maximum baseline value is less than or equal to 1X ULN,
    - patients whose maximum baseline is greater than 1X ULN but less than 3X ULN,
    - patients whose maximum baseline value is greater than or equal 3X ULN, and
    - patients whose baseline values are missing.
- The analysis of any postbaseline ALT (AST) ≥5X ULN will be contain 5 baseline subsets:
    - patients whose non-missing maximum baseline value is less than or equal to 1X ULN,

  - patients whose maximum baseline is greater than 1X ULN but less than 3X ULN,
  - patients whose maximum baseline is greater than or equal to 3X ULN but less than 5X ULN,
  - patients whose maximum baseline value is greater than or equal to 5X ULN, and
  - patients whose baseline values are missing.

- The analysis of any postbaseline ALT (AST) ≥10X ULN will contain 6 baseline subsets:
  - patients whose non-missing maximum baseline value is less than or equal to 1X ULN,
  - patients whose maximum baseline is greater than 1X ULN but less than 3X ULN,
  - patients whose maximum baseline is greater than or equal to 3X ULN but less than 5X ULN,
  - patients whose maximum baseline is greater than or equal to 5X ULN but less than 10X ULN,
  - patients whose maximum baseline value is greater than or equal to 10X ULN, and
  - patients whose baseline values are missing.
- The analysis of any postbaseline total bilirubin ≥2X ULN will contain 4 baseline subsets:
  - patients whose non-missing maximum baseline value is less than or equal to 1X ULN,
  - patients whose maximum baseline is greater than 1X ULN but less than 2X ULN,
  - patients whose maximum baseline value is greater than or equal to 2X ULN, and
  - patients whose baseline values are missing.
- The analysis of any postbaseline ALP ≥2X ULN will contain 4 baseline subsets the same as above for total bilirubin

For the above elevation analysis, maximum baseline and maximum postbaseline will be used. Maximum baseline is defined as the maximum non-missing observation in the baseline period. The maximum postbaseline is defined as the maximum non-missing postbaseline measurements including scheduled, unscheduled and retest measurements.

A listing of patients with any post randomization

- elevation of serum ALT to ≥5-fold ULN on 2 or more consecutive blood tests

- elevated serum TBL to ≥2-fold ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2-fold ULN on 2 or more consecutive blood tests
- study participant discontinued from treatment due to a hepatic event
- hepatic event considered to be an SAE

will be provided, including demographics, disposition, study drug exposure, AEs, concomitant medications, all the liver measurements (ALT, AST, total bilirubin, ALP and GGT). The time course plot of ALT, AST, ALP, TBL and GGT will also be provided for the patients meeting the above criteria.

5.10.6. Electrocardiograms

Electrocardiograms will be collected at specific study visits. For Visit 3, 6, 9, 15 and 17, a triplicate ECG will be collected. The other visits, a single ECG will be collected. The average values will be used in the analysis.

The actual and change from baseline for selected ECG parameters (heart rate and intervals) will be analyzed using the MMRM model. The MMRM model will be used for the analysis during the treatment period and will contain the term for treatment, baseline value, visit, and visit-by-treatment interaction as factors, patient as random effect, and compound symmetric as the variance-covariance structure. The last nonmissing measurements will also be analyzed by the ANCOVA model with treatment and baseline value as covariates.

5.10.7. Immunogenicity

The sample to determine antibody against LY3209590 will be collected at protocol-specified visits. Treatment emergent anti-drug antibodies (TEADA) can be subclassified as either treatment induced (baseline antibody level is not detected) or treatment boosted (baseline antibody level is detected):

- treatment induced response: a postbaseline titer ≥ 2-fold the minimum required dilution (1:20) if the baseline status is not detected (i.e., titer less than the minimum required dilution)
- treatment boosted response: a postbaseline titer ≥ 4-fold of the baseline titer if the baseline status is detected. For an example, 1:20 at baseline and 1:80 post baseline is treatment boosted.

The frequency and percentage of a participant's baseline ADA status for patients with baseline and at least one postbaseline measurement, allowing TEADA evaluation, will be summarized.

The TEADA status will be determined by all postbaseline data. The number and percentage of patients with positive TEADA response any time after randomization including the treatment period and follow-up period will be summarized by treatment group.

A listing of anti-LY3209590 antibodies at each visit will be provided for the Safety Population. The listing will include anti-LY3209590 antibody status (detected/not detected), the titer for detected samples and the TEADA status.

5.11. FGM Analysis

5.11.1. General Consideration

The FGM system will be offered to all participants meeting study entry criteria except for reporting of screening clinical laboratory assessments in Study I8H-MC-BDCL (BDCL). Participants will undergo 3 FGM sessions using the LibrePro System (Abbott) in the 14-day period prior to randomization, Visit 15, and Visit 20. Patients will remain blinded to these assessments until the study is completed.

All patients who are randomized to either LY3209590 Algorithm 1 or insulin degludec receive at least 1 dose of study treatment, and have FGM data from baseline and at least 1 postbaseline collection period will be included in the analyses. The data collected after permanent discontinuation of the IP will be censored. There will be no multiplicity adjustment. Additional analysis may be conducted to compare between the LY3209590 (by pooling LY3209590 Algorithm 1 and LY3209590 Algorithm 2) and insulin degludec if deemed necessary.

According to the 2020 American Diabetes Association standard of medical care in diabetes, the FGM data will be included in the analysis only if at least 70% of the total measures in the analysis period are obtained (defined as a valid FGM period). For example, the 24-hour period will have 96 measures and the minimum number of measures will be 68. All the FGM derivations are based on the data from valid FGM period unless otherwise specified.

The FGM variables will be derived for each FGM day when the analysis data meeting the above requirement. The derived variables for a visit will be based on the daily FGM variables within the given visit.

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

5.11.2. FGM Variable and Analysis

The continuous variables derived from FGM will be summarized and compared between treatment groups by visit using MMRM model. The model will include the treatment, HbA1c stratum (<8.5% or >=8.5%), baseline value of the dependent variable, visit, and treatment by visit interaction. The raw mean and LS mean difference between treatment groups will be summarized.

For the between-day and within-day glucose variability, the variable will take log-transformation before performing the MMRM analysis.

The binary variables will be analyzed using a longitudinal logistic regression. In the longitudinal logistic regression model, the independent variables of treatment, baseline HbA1c value, baseline continuous variable corresponding to the binary dependent variable, visit, and treatment by visit interaction will be used.

For the hypoglycemia episodes defined by FGM, the analysis using a negative binomial model with the offset of log (exposure in year) will be performed. The model will include treatment and baseline HbA1c.

5.11.2.1. Hypoglycemia

- 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 (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<54 mg/dL [3.0 mmol/L]) during the nighttime period, the daytime and a 24-hour period.
- Percentage and Duration (in minutes) of time per day where glucose values are within a hypoglycemic range (defined as 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.
- Incidence of hypoglycemic episodes (defined as <70 mg/dL [3.9 mmol/L], or <54 mg/dL [3.0 mmol/L] or <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.
- Rate of hypoglycemic episodes (defined as <70 mg/dL [3.9 mmol/L], or <54 mg/dL [3.0 mmol/L] or <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.
- Duration (in minutes) of each individual hypoglycemic episode (defined as <70 mg/dL [3.9 mmol/L], or <54 mg/dL [3.0 mmol/L] or <70 mg/dL [3.9 mmol/L] and ≥54 mg/dL [3.0 mmol/L] for at least 30 minutes).

5.11.2.2. Hyperglycemia

- Percentage and Duration (in minutes) of time per day glucose values are within a hyperglycemic range (defined as >180 mg/dL [10.0 mmol/L] 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.

5.11.2.3. Normal Range

Percentage and Duration (in minutes) of time per day glucose values are within a normal 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.

5.11.2.4. Glycemic Variability

- Low Blood Glucose Index (LBGI) during the nighttime period and a 24-hour period.
- High Blood Glucose Index (HBGI) during the nighttime period and a 24-hour period.
- Combined blood glucose risk index (BGRI derived as LBGI + HBGI) during the nighttime period and a 24-hour period.
- Within-day and between-day glucose coefficient of variation (CV) during the nighttime period and a 24-hour period.
- Within-day and between-day glucose coefficient of variation (CV) ≤36% during the nighttime period and a 24-hour period.
- Within-day and between-day glucose SD during the nighttime period and a 24-hour period.
- Mean of daily differences (MODD) during the nighttime period and a 24-hour period.

5.11.2.5. Ambulatory Glucose Profile

The ambulatory glucose profile (AGP) during the 24-hour period will be generated with interquartile ranges, at treatment-group level by visit (baseline, Week 12 and Week 26), based upon the observed FGM measures.

5.11.2.6. FGM Targets of Glycemic Control

According to the guidance (Battelino 2019), the following FGM 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]) >70%
- The percentage of time within a hypoglycemic range (defined as defined as <70 mg/dL [3.9 mmol/L]) <4%
- The percentage of time within a hypoglycemic range (defined as 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%

5.11.3. Definition of Variables

In this section, we define the derived variables that are used for the analysis in Section 5.11.2 and some additional variables that may be used for exploratory analyses.

5.11.3.1. Glucose in Target Ranges, Hypoglycemia or Hyperglycemia

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

5.11.3.2. Hypoglycemic Episode

The FGM-determined hypoglycemic episode is defined as glucose <54 mg/dL (or ≤ 70 mg/dL) for at least 30 minutes.

The duration of each episode will be calculated using the time difference between the 2 time points before the incidence starts and after the incidence ends.

The average duration will be calculated by dividing the sum of the duration of individual episodes during the given visit by the number of episodes.

The FGM-determined nighttime hypoglycemic episode is defined as hypoglycemic episodes that occur between 2400 hours and 0600 hours. To calculate the duration of nighttime hypoglycemic episode, the end date/time will be the end date/time when the patient passes outside the hypoglycemic range even if it is outside the interval of 2400 hours and 0600 hours.

5.11.3.3. Glycemic Variability

Glycemic variability will be evaluated using the notation below:

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

n represents the number of time points within the time period

k represents a day within a visit

m represents number of days FGM is performed at a visit

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

- Within-Day Variability

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

Within-day glucose SD (Rodbard 2009):

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

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

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

The LBGI, HBGI, and BGRI will be calculated using the standard formulas.

The LBGI has been developed to quantitate both frequency and severity of hypoglycemia. The LBGI has been validated as a predictor of severe hypoglycemia, which is an SAE and could result in coma or death if unrecognized and untreated. The HBGI quantifies both frequency and severity of hyperglycemia and has been related to HbA1c and risk for hyperglycemia (Kovatchev et al. 2006). Additionally, both the LBGI and HBGI have a high sensitivity to changes in glycemic profiles and control (Kovatchev et al. 2006). LBGI is a non-negative number that increases as the number of low readings increases. HBGI is a non-negative number that increases as the number of high readings increases.

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

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

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

This transforms the BG data using a nonlinear transformation that maps the BG range of 20 to 600 mg/dL to a symmetric interval of $\left(-\sqrt{10}, \sqrt{10}\right)$

The center of the BG scale is 112.5 mg/dL and is mapped to 0

Step 2: Compute BG risk for each reading

$rl(BG_i) = 10 \times f(BG_i)^2$ if $f(BG) < 0$; otherwise $rl(BG_i) = 0$

$rh(BG_i) = 10 \times f(BG_i)^2$ if $f(BG) > 0$; otherwise $rh(BG_i) = 0$

Assign the risk of each BG value by applying the above quadratic risk function

Value range from 0 (achieved when BG = 112.5, the center) to 100

Left side of the parabola is risk of hypoglycemia, and the right side is risk of hyperglycemia

Step 3: Compute LBGI and HBGI

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

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

Step 4: Compute BGRI

$BGRI = LBGI + HBGI$

- Between-Day Variability

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

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

5.12. Subgroup Analyses

The subgroups will be defined as:

- Body mass index (<30, ≥30)
- Baseline HbA1c (<8.5% and >=8.5%)
- Baseline HbA1c (defined by baseline median)
- Concomitant medication (metformin alone and metformin in combination with other oral antidiabetic medications)

The outcome measures included in the subgroup analyses are:

- HbA1c and change in HbA1c from baseline to up to 26 weeks
- Documented hypoglycemia, non-nocturnal, and nocturnal hypoglycemia rates (glucose <70 mg/dL [3.9 mmol/L] and glucose ≥54 mg/dL [3.0 mmol/L]) during 0-26 weeks.

Analyses for HbA1c and its change will be performed examining the 3-way interaction of the primary treatment arms, visit and the subgroup variable using the same MMRM model described for the primary analysis. This model will include the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit, and the subgroup.

The hypoglycemia rates will be analyzed using a negative binomial regression including the treatment, baseline HbA1c, subgroup, 2-way interaction of subgroup and treatment as covariates, and log (exposure in year) as the offset.

The interaction effects will be evaluated using a significance level of 0.1, unadjusted. If the interaction effect is significant ($p<0.1$), separate analysis without the terms related with the subgroup will be performed for each subpopulation.

5.13. Interim Analyses

6. Unblinding Plan

This is an open-label study where investigators and patients are aware of their assigned treatment.

LY3209590 was designed as a novel, once-weekly, long-acting insulin. The dose algorithm was developed by PK/PD information of LY3209590 and modification may be needed. The study team is unblinded to the study treatment to monitor patient safety and provide dose instruction to investigator if needed.

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8. Appendices

Appendix 1. 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 the insulin naïve population, the patient-reported hypoglycemia data could be sparse, so that 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

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

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

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

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