I8H-MC-BDCM Statistical Analysis Plan Version 2

A Phase 2, Randomized, Open-Label Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants with Type 2 Diabetes Mellitus Previously Treated with Basal Insulin

NCT03736785

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1. Statistical Analysis Plan for Protocol I8H-MC-BDCM: Evaluate the Safety and Efficacy of LY3209590 in Patients with Type 2 Diabetes Mellitus Previously Treated with Basal Insulin

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 approximately 375 patients with type 2 diabetes mellitus treated with basal insulin.

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Protocol I8H-MC-BDCM
Phase 2

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below
Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 31-January-2019.

Approval Date: 16-Mar-2020 GMT

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Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on 31 January 2019. Version 1 was based on the Protocol I8H-MC-BDCM approved on 31 August 2018.

This SAP is the second version approved prior to the final database lock. The main changes are listed below:

- Correcting mistakes in the first version (for examples, MMRM model terms for the primary and secondary outcome, and significant level for treatment effect tests)
- Removing duplicated information/analysis in the same section to avoid confusion
- Updating analysis details to be consistent with other Phase 2 studies in the same program (for example, the definition of Safety Population)
- Replacing the multiple imputation method for the analysis of HbA1c meeting the target with longitudinal logistic regression
- Adding required safety analyses which were missing in the first version (for example, analysis of body weight and analysis of treatment emergent antidrug antibody status)
- Providing analysis details to clarify the analysis input data (for example, the SMQ search criteria for hepatobiliary events)
- Modifying analyses to ensure using the collected data as the input data (for example, CGM analyses using available baseline variables as covariates)

3. Study Objectives

3.1. Primary Objective

To evaluate the efficacy of LY3209590, especially the change in hemoglobin A1c (HbA1c) from baseline to 32 weeks of treatment in patients with Type 2 diabetes mellitus (T2DM) treated with basal insulin alone or in combination with oral anti-hyperglycemic medication(s).

3.2. Secondary Objectives

3.2.1. Efficacy

To compare the efficacy of LY3209590 versus insulin Degludec treatment groups for the following:

1. HbA1c change from baseline to Week 12 and 32;
2. Fasting glucose change from baseline to Week 12 and 32;
3. Insulin dose change from baseline to Week 12 and 32.

3.2.2. Safety

To compare the safety of LY3209590 versus insulin Degludec treatment groups for the following:

1. Documented, documented nocturnal and severe hypoglycemia incidence and rates during the treatment period (0-12, 12-32, and 0-32 weeks);
2. Treatment-emergent serious adverse events (SAEs) incidences;
3. Body weight change from baseline at Week 12 and 32.

3.3. Exploratory Objectives

1. Fasting serum glucose (FSG) by laboratory and change from baseline to Weeks 6, 12, 18, and 32 and all other scheduled visits;
2. Fasting blood glucose (FBG) by self-monitored blood glucose (SMBG) and change from baseline at Weeks 12 and 32 and all other available visits;
3. Fasting blood glucose (FBG) intra-patient variability (by SMBG) at Weeks 12 and 32 and all other available visits;
4. Six-point SMBG profile (pre-meal and 2-hour postprandial SMBG measurements for the morning, midday, and evening meals in 1 day.) at Visit 6, 9, 12, 15, 17, 20, 21;
5. Proportion of patients with HbA1c <7.0% at 12 and 32 weeks;
6. Proportion of patients with HbA1c ≤6.5% at 12 and 32 weeks;
7. Triglycerides, free fatty acid (FFA), liver aminotransferase (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]) change from baseline to Weeks 6, 12, and 32;
8. Discontinuation of investigational product (IP) due to AEs;
9. Clinical laboratory results;

10. Number of dose adjustments to steady-state;
11. Antibodies to LY3209590;
12. Incidence and rate of documented non-nocturnal hypoglycemia during the treatment period (0-12, 12-32, and 0-32 weeks);
13. Incidence and rate of hypoglycemia during the treatment period (0-12, 12-32, and 0-32 weeks) by continuous glucose monitoring (CGM);
14. Glucose time in target range, time in hyperglycemia, time in hypoglycemia during the treatment period (0-12, 12-32, and 0-32 weeks) by CGM;
15. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and change from baseline to Weeks 6, 12, and 32.

4. A Priori Statistical Methods

4.1. 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 Lilly. 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 in the clinical study report (CSR). Additional exploratory analyses will be conducted, as deemed appropriate.

Unless otherwise specified, listings will be ordered by the patient ID nested within the investigator site.

The patient populations used for this study are described below:

Population and Analysis Set	Description
Entered/Enrolled Population	All study participants who sign informed consent
Randomized Population	All study participants who are randomly assigned a treatment arm
Efficacy analysis set (EAS)	Data for all randomized study participants who receive at least one dose of study medication, excluding data after using rescue medication(not acute therapy) or stopping study medication (last dose date + 10 days). In the event of a treatment error, participants will be analyzed according to the treatment they actually received.
Safety Population	All randomized study participants who receive at least one dose of study medication.
CGM Population	All randomized study participants who receive at least 1 dose of study medication, and have CGM data from at least 1 collection period.

Abbreviations: CGM = continuous glucose monitoring.

Safety analyses will be conducted using the Safety Population with all data collected during the study including treatment and follow-up period regardless of the treatment disposition status. Efficacy analyses will be conducted on the efficacy analysis set (EAS), unless otherwise specified.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.10 and confidence intervals (CIs) will be calculated at 90%, 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

Baseline value for a variable is defined as the last nonmissing value for this variable prior to or at randomization visit (Visit 3), unless otherwise specified.

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 percentages. 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 for 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, all 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.

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

4.2. Patient Disposition

The reasons for discontinuation from the study and discontinuation of the study treatment will be summarized for the Randomized Population by treatment group and compared between the treatment groups using Fisher's exact test. Similar summary without treatment comparison will be provided for the discontinuation reasons prior to randomization.

A listing of the primary reason for patient discontinuation from the study or patient discontinuation of the treatment medication will be generated for the All Randomized Population.

A listing of the randomization codes for this study will be provided.

4.3. 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 (<7%, ≥7% and <8.5%, ≥8.5%), fasting serum glucose (FSG: mmol/L and mg/dL), lipid measures (triglycerides, FFA, total cholesterol, HDL-C, and LDL-C), liver enzymes (ALT, AST and total bilirubin), HbA1c strata (HbA1c ,8.5% and ≥8.5% at Visit 1), and sulfonylureas [SU] use will be summarized by treatment group using the All Randomized Population. 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-patient listing of demographic and selected baseline characteristics will be provided for all randomized patients.

Number of randomized patients and number of 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.

4.4. Concomitant Medications

Concomitant medications will be summarized by treatment group and will be compared between treatment groups using Fisher's exact test for all randomized patients. 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.

Listing of concomitant medications will be provided.

4.5. Treatment Compliance

Treatment compliance will be summarized using the EAS. For a given study participant, overall compliance for treatment period is based on the ratio of the total number of doses taken to the total number of required doses. If the ratio is less than 80%, the participant will be considered as treatment non-compliant. The compliance difference between treatment groups will be evaluated using Fisher's exact test.

Adherence to the dosing algorithm is required from Visit 3 (Randomization) up to Visit 21. The number and percentage of investigator-calculated doses that are not equal to patient actual dose will be provided.

4.6. 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 all randomized patients. The listing of IPDs for all randomized patients will also be provided.

The list of pre-defined important protocol deviation was provided in the trial issue management plan. The decision and rationale for not reporting certain protocol deviations as important in the CSR will be documented in the study decisions log.

4.7. Primary Outcome and Methodology

The primary efficacy measure of change in HbA1c at Week 32 (together with HbA1c measure at other postbaseline visits) will be summarized and analyzed using an MMRM approach on the EAS. This model implicitly adjusts for missing data through a variance-covariance structure. This model will include the fixed effects of treatment (LY3209590 Algorithm 1, LY3209590 Algorithm 2, insulin degludec), stratification factors (country, BMI strata [BMI <30 or ≥30], sulfonylureas use[Y/N]), visit, treatment by visit interaction, and 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 for the LS mean for the individual treatment arms, treatment LS mean difference (LY3209590 Algorithm 1 vs. insulin degludec, LY3209590 Algorithm 2 vs insulin degludec, and LY3209590 Algorithm 1 vs LY3209590 Algorithm 2) in the change in HbA1c at 32 weeks will be constructed. Similar summary will be provided for the comparison between pooled LY arm and insulin degludec based on the contrast from the above MMRM model.

4.8. Secondary and Additional Efficacy Analyses

The analysis population for the secondary analysis on HbA1c reduction is the EAS. Treatment comparison at 32 weeks will be used to assess the difference between the pooled LY arm and Degludec arm. The 2-sided 90% CI for the LS mean of the difference between pooled LY arm and Degludec arm in the change in HbA1c at 32 weeks will also be constructed.

A sensitivity analysis will be conducted to evaluate the “treatment policy” estimand, which is defined as the treatment differences in HbA1c at 32 weeks with the randomized treatment based

on all randomized patients who took at least one dose of study medication, and have baseline and at least one postbaseline measurement. In this analysis, all endpoint data regardless of treatment disposition status will be included and missing data will be imputed using multiple imputations to assess sensitivity to departures from the missing at random assumption. More specifically, the missing endpoint will be imputed multiple (for example, 100) times using the baseline data. Then, the inference based on the multiple imputations framework will be used (Rubin 1987).

The following secondary and additional efficacy analyses will be performed 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) by SMBG and change from baseline at Weeks 12 and 32;
3. Fasting serum glucose (FSG) by laboratory and change from baseline at Weeks 6, 12, 18, and 32;
4. Between-day glucose variability measured by the SD of the FBG (SMBG) at Week 12 and 32;
5. Six-point SMBG profile (pre-meal and 2-hour postprandial SMBG measurements for the morning, midday, and evening meals in 1 day) at Weeks 12 and 32. Since the baseline SMBG profile is not collected, the baseline FBG instead of baseline value of the dependent variable will be used as a covariate.
6. Within-day and between-day glucose variability measured by the standard deviation (SD) of 6-point SMBG. Since the baseline SMBG profile is not collected, the baseline SD of FBG instead of baseline value of the dependent variable will be adjusted as a covariate.

The proportion of the patients with HbA1c <7.0% (or ≤6.5%) will be analyzed using a longitudinal logistic regression. In the longitudinal logistic regression model, the independent variables of treatment, country, BMI strata (BMI <30 or ≥30), baseline SU use (yes or no), baseline HbA1c value, visit, and treatment by visit interaction will be used.

The insulin dose units are different between LY3209590 (mg) and insulin degudec (unit). Therefore, descriptive statistics will be provided for the insulin dose and the dose change from baseline. No treatment comparison will be conducted.

4.9. Pharmacokinetic/Pharmacodynamic Analyses

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

4.10. Safety Analyses

Safety measures will include AEs, vital signs, treatment exposure, adjudicated cardiovascular events, laboratory measures, and antibodies to LY3209590. Safety analysis will be reported for Safety Population and data measured while on treatment and after study drug discontinuation will be included.

4.10.1. Study Drug Exposure

Exposure in days in the study will be calculated for each patient and summarized by treatment group. The mean of exposure will be compared between treatment groups using 2-sample *t*- test. 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 last dose date + 7 days for LY3209590 to account for the weekly injection). 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/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, median, sum in total patient years, minimum and maximum) by treatment group.

The duration on study from date of 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, median, sum in total patient years, minimum and maximum.

A by-patient listing of drug exposure data will be created to provide data for the CSR appendix of Compliance and/or Drug Concentration Data.

4.10.2. Adverse Events (AEs)

Adverse events will be summarized as treatment emergent AEs (TEAEs, defined as events that are newly reported after the first dose of study basal insulin or reported to worsen in severity from baseline) for the Safety Population and compared between treatments unless otherwise specified. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) will be used in determination of 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 to the end of the study (up to Visit 801).

The number and percentage of patients with TEAEs will be summarized by treatment using MedDRA PTs nested within System Organ Class (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.

A TEAE considered possibly related to study drug will be summarized, separately, by treatment group using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

A by-patient listing of all AEs for the Safety Population will be created including, but not limited to, SOC, event PT, severity, and relationship to study drug for all randomized patients.

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

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

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

4.10.3. 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

4.10.3.1. Death and Nonfatal Cardiovascular Events

Deaths and nonfatal cardiovascular AEs will be adjudicated by an independent Clinical Endpoint Committee. The following events will be adjudicated and listed by patient for all randomized population: death due to cardiovascular events, myocardial infarction (MI), hospitalization for unstable angina, stroke, or transient ischemic attacks (TIA). 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.

4.10.3.2. Hypoglycemia Events

Both the rate per 1 patient year and incidence of the following type of hypoglycemia events will be derived and analyzed: documented hypoglycemia, documented nocturnal hypoglycemia (occurs between bedtime and waking), and documented non-nocturnal hypoglycemia (occurs between waking and bedtime). .

Table BDCM.1 provides the summary of statistical method for hypoglycemia event related analysis. Additionally, severe hypoglycemia events will be listed, and incidence of severe hypoglycemia will be compared between treatments using Fishers' exact test.

Table BDCM.1. Hypoglycemia Event Related Analyses

Endpoint	Time Point*	Statistical Method
Rate of hypoglycemia events defined by glucose <54 mg/dL (3.0 mmol/L) and ≤ 70 mg/dL (3.9 mmol/L) • Documented • Nocturnal • Non-Nocturnal	0-12, 0-32, 12-32 weeks, post-treatment period (up to Visit 801)*	Negative binomial regression with treatment, baseline SU use (yes/no), baseline HbA1c,baseline hypoglycemia event rate with the same category of the dependent variable, log (exposure in year) as the offset in the model.
Incidence of hypoglycemia events defined by glucose <54 mg/dL(3.0 mmol/L) and ≤ 70 mg/dL (3.9 mmol/L) • Documented • Nocturnal • Non-Nocturnal	0-12, 0-32, 12-32 weeks, post-treatment period (up to Visit 801)*	Logistic regression with treatment, baseline SU use (yes/no), baseline HbA1c, baseline hypoglycemia event rate with the same category of the dependent variable in the model. Note that the logistic regression will be conducted when ≥10 patients with this event.
• Proportion of patients with HbA1c <7% without nocturnal hypoglycemia event • Proportion of patients with HbA1c ≤6.5% without nocturnal hypoglycemia event	0-32 weeks	Logistic regression with treatment, baseline SU/meglitinide use (yes/no), baseline HbA1c,and baseline nocturnal hypoglycemia event rate in the model.

Abbreviations: HbA1c = hemoglobin A1c.

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 1 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.

The following is the example of the SAS code of the negative binomial regression for analyzing the rate of hypoglycemia events.

```
proc glimmix empirical data=DATA;
class TREATMENT;
  model HYPO_FREQ=TREATMENT [BASELINE_HYPO_RATE]
            /dist=nb link=log offset=log(exposure in
days/365.25);
        lsmeans TREATMENT/OM pdiff cl alpha=0.1 ilink;
        random _residual_;
run;
```

4.10.3.3. 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)

4.10.3.4. 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 BDCM.2 contains a list of MedDRA PTs based on MedDRA 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 the PTs in Table BDCM.2 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 BDCM.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
Injection site bruising	10022052	Broad
Injection site haematoma	10022066	Broad
Injection site haemorrhage	10022067	Broad
Injection site pain	10022086	Broad

4.10.3.5. 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.

4.10.4. Laboratory Measures

The data from laboratory testing will be summarized by treatment 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 selected lab measures, log-transformed value will be used in MMRM, and the geometric LS means as well as the percentage change from baseline will be reported.

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 of patients in the safety population who had an abnormal laboratory value during the study will be provided, including the actual measurement (in both SI and CN unit), abnormal result, and reference low or high limits.

4.10.4.1. Lipid Measures

Triglycerides, total cholesterol, LDL-C, and HDL-C (results from fasting samples) will take log-transformation before being analyzed by MMRM model define above for the Safety population.

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).

4.10.4.2. 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]) measures will take log-transformation before performing the MMRM analysis. 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 subsest 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 TBL ≥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.

A listing of patients with any post randomization

- elevation of serum ALT to ≥3-fold ULN on 2 or more consecutive blood tests
- elevation of serum ALT to ≥5-fold ULN on 2 or more consecutive blood tests
- elevation of serum AST to ≥3-fold ULN / 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 or abnormality of liver tests
- hepatic event considered to be an SAE

will be provided, including the actual measurement of ALT, AST, TBL, ALP, and the corresponding reference of high limits.

4.10.5. Vital Signs and Body Weight

Vital signs and weight will be summarized by treatment and visit. Change from baseline (last nonmissing value up to Visit 3) to postbaseline value for vital signs and weight will be summarized 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.

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 BDCM.3 will be used to define the low and high limits and change thresholds.

Table BDCM.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.

4.10.6. Antibodies

4.10.6.1. Anti-LY3209590 Antibodies

The sample to determine antibody against LY3209590 will be collected at protocol-specified visits. Treatment emergent antidrug 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 titer 2-fold (1 dilution) greater than the minimum required dilution (1:20) if the baseline level is not detected (i.e., titer less than the minimum required dilution)
- treatment boosted response: a 4-fold (2dilution) increase in titer compared to baseline if the baseline level is detected. For an example, 1:20 at baseline and 1:80 post baseline is treatment boosted.

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.

4.10.7. Electrocardiograms

Electrocardiograms (ECGs) will be collected at specific study visits. For screening visit, a single ECG will be collected. For the other scheduled visits, a triplicate ECG will be performed and the average values will be used in the analysis.

The actual and change from baseline for selected ECG parameters (heart rate, PR auto global beat, QRS, QT and QTcF) 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.

4.11. Continuous Glucose Monitoring Analysis

4.11.1. General Consideration

The continuous glucose monitoring system will be offered to all patients at selected sites in Study I8H-MC-BDCM. Interstitial glucose (ISIG) values will be collected by the CGM at 5-minute intervals. Continuous glucose monitoring recordings will be obtained for all patients throughout the treatment phase of the study. The device readings and alarms will not be blinded to the patients so that they can be warned of hypoglycemia and appropriately manage any hypoglycemic episodes.

All patients who are randomized to 1 of the study treatments (LY3209590 Algorithm 1, LY3209590 Algorithm 2, insulin degludec) receive at least 1 dose of study treatment, and have CGM data from at least 1 collection period which will be included in the analyses. The data collected after permanent discontinuation of investigational product will be censored. There will be no multiplicity adjustment. Since the sensor takes about 2 hours to reach the steady state after insertion, it is recommended to only use the steady state data for analysis.

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

4.11.2. CGM Variable and Analysis

The following variables derived from CGM 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 FBG, visit, and treatment by visit interaction. The LS

mean difference between treatment groups will be summarized. We are missing CGM documentation if visit intervals are longer than 4 weeks due to storage limitation in the receiver.

4.11.2.1. 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).
- Percentage and Duration (in minutes) of time per day glucose values are within a hypoglycemic range (defined as ≤70 mg/dL [3.9 mmol/L]) during 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.
- 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 a 24-hour period.
- Incidence of hypoglycemic episodes during the nocturnal period and during a 24-hour period.
- Rate of hypoglycemic episodes per patient per year during the nighttime period and during a 24-hour period.
- Duration (in minutes) of each individual hypoglycemic episode.

4.11.2.2. 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] during a 24-hour period.

4.11.2.3. Normal Range

- Percentage and Duration (in minutes) of time per day glucose values are within a normal glycemia range (defined as between 71 mg/dL and 180 mg/dL [3.9 and 10.0 mmol/L]) inclusive during a 24-hour period.
- Percentage and Duration (in minutes) of time per day glucose values are within a normal glycemia range (defined as between 71 mg/dL and 140 mg/dL [3.9 and 7.8 mmol/L]) inclusive during a 24-hour period.

4.11.2.4. Glycemic Variability

- Low Blood Glucose Index (LBGI) during the nighttime period and during a 24-hour period.
- High Blood Glucose Index (HBGI) during the nighttime period and during a 24-hour period.
- Combined blood glucose risk index (derived as LBGI + HBGI) during the nighttime period and during a 24-hour period.
- Within-day and between-day glucose coefficient of variation during the nighttime period and during a 24-hour period.
- Within-day and between-day glucose SD during the nighttime period and during a 24-hour period.

4.11.3. Definition of Variables

In this section, we define the derived variables that are used for the analysis in Section 4.11.2 and some additional variables that may be used for exploratory analyses.

4.11.3.1. 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).

4.11.3.2. Hypoglycemic Episode

The CGM-determined hypoglycemic episode is defined as ISIG meeting the hypoglycemia range (e.g., <54 mg/dL or ≤ 70 mg/dL) for at least 15 minutes and the end of a hypoglycemic episode is defined as the absence of sensor readings ≥54 mg/dL for 15 minutes or more. The linear interpolation method will be used to determine the start/end time when the patient's glucose value crossed the glucose threshold.

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 CGM-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.

4.11.3.3. 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 CGM 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):

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

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

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

Inter-quartile range (IQR) (Mazze et al. 2008):

$$IQR = \frac{1}{m}\sum_{k=1}^{m} IQR_k = \frac{1}{m}\sum_{k=1}^{m} (75\text{th} - \ 25\text{th percentile of all BG values on day k})$$

- 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):

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

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.

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

- Overall Variability

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

- Risk for Hypo/Hyperglycemia

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). The LBGI is a non-negative number that increases as the number of low readings increases. The HBGI is a non-negative number that increases as the number of high readings increases.

The LBGI, HBGI, and blood glucose risk index (BGRI) will be derived for each day of a visit and for overall in 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

$\text{rl}\left(\text{BG}_i\right) = 10 \times \text{f}\left(\text{BG}_i\right)^2$ if f(BG) < 0; otherwise $rl(BG_i) = 0$

$\text{rh}\left(\text{BG}_i\right) = 10 \times \text{f}\left(\text{BG}_i\right)^2$ 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

4.12. Subgroup Analyses

The subgroups will be defined as:

- Body mass index (<30, ≥30)
- Baseline HbA1c (<8.5% and >=8.5%)

The outcome measures included in the subgroup analyses are:

- HbA1c and change in HbA1c from baseline to up to 32 weeks
- Documented hypoglycemia and nocturnal hypoglycemia rates (<54 mg/dL [3.0 mmol/L]) during 0-32 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 same fixed effects for hypoglycemia event analyses plus factors of subgroup, 2-way interaction of subgroup and treatment.

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.

4.13. Interim Analyses

Study team will conduct routine unblinded program-level safety reviews and some selected efficacy data reviews.

An interim analysis of select safety, efficacy, and PK data is planned when approximately 50% of study participants complete 6 weeks of treatment. Results of interim analysis might be used for adjusting LY3209590 dosing algorithm.

A subsequent interim analysis of select safety, efficacy, and PK data is planned when all study participants complete 12 weeks of treatment. The analyses for the primary objective and

secondary objectives, and some other key endpoints will be conducted at that time. Results of interim analysis will be used to design subsequent studies.

Additional unplanned interim analyses may be performed as necessary, and the rationale for the interim analysis will be documented in the clinical study report. The analyses for the primary objective and secondary objectives, and some other key endpoints were conducted at that time.

5. Unblinding Plan

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

6. References

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