I8B-MC-ITSD Statistical Analysis Plan Version 2

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro in Combination with Insulin Glargine or Insulin Degludec, in Adults with Type 1 Diabetes

NCT03952130

Approval Date: 18-Jan-2022

1. Statistical Analysis Plan: I8B-FH-ITSD: A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro in Combination with Insulin Glargine or Insulin Degludec, in Adults with Type 1 Diabetes

LY900014

Study I8B-FH-ITSD is a Phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter, parallel, active-controlled study conducted in patients with type 1 diabetes currently using a multiple daily injection regimen.

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Protocol I8B-FH-ITSD
Phase 3

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

Approval Date: 18-Jan-2022 GMT

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3. Revision History

Statistical analysis Plan (SAP) Version 1 was approved prior to the first patient visit. Version 1 was based on the Protocol I8B-FH-ITSD (ITSD) approved on 13 July 2018.

The main changes of the second version are listed below.

- Analysis period of from randomization to Week 26 (including all data regardless of IP use) was added for some of the safety analysis.
- Removed the baseline rate covariate from all hypoglycemia models as there were many critical outliers leading to inaccurate in the LSM and the biases were inconsistent.
- Summaries of postmeal hypoglycemia < 54 mg/dL were added.
- Summaries of postmeal hypoglycemia occurring >4 hours after start of a meal were added.
- COVID-19 related analyses were added.
- Summaries of pre-study insulin treatment type between treatment groups were added.
- The graphical testing scheme has been revised according to the simulation and optimization analysis results.

4. Study Objectives

Table 4.1 shows the objectives and endpoints of the study.

Table 4.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
1. (H1) To test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control (NIM=0.4% for HbA1c) in patients with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec for 26 weeks	1. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Multiplicity Adjusted Objectives	
2. (H2) To test the hypothesis that LY900014 is superior to insulin lispro in controlling 1-hour PPG excursions, when administered as prandial insulin	2. Difference between LY900014 and insulin lispro in the 1-hour PPG excursion (serum glucose measured 1 hour after the start of the meal minus fasting serum glucose) from an MMTT at Week 26
3. (H3) To test the hypothesis that LY900014 is superior to insulin lispro in controlling 2-hour PPG excursions, when administered as prandial insulin	3. Difference between LY900014 and insulin lispro in the 2-hour PPG excursion (serum glucose measured 2 hours after the start of the meal minus fasting serum glucose) from an MMTT at Week 26
4. (H4) To test the hypothesis that LY900014 is superior to insulin lispro on improving glycemic control (HbA1c) when administered as prandial insulin	4. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
5. To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	5. Rate (events/patient/100 years) of severe hypoglycemic events from baseline through Week 26

Objectives and Endpoints

Objectives	Endpoints
Other Secondary Objectives (continued)	
6. To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic postmeal hypoglycemia	6. Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic postmeal hypoglycemia within 1 and 2 hours after start of a meal from Week 12 through Week 26, Week 0 through Week 26
7. To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic hypoglycemia	7. Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 events) of documented symptomatic hypoglycemic events from Week 12 through Week 26, Week 0 through Week 26
8. To compare LY900014 and insulin lispro with respect to 1,5-AG	8. Change from baseline 1,5-AG values at Week 26
9. To compare LY900014, and insulin lispro with respect to 10-point SMBG profiles	9. Change from baseline 10-point SMBG values at Week 26
10. To compare LY900014 and insulin lispro with respect to total, basal, and prandial insulin dose	10. Change from baseline in total, basal and prandial insulin doses and prandial/total insulin dose ratios at Week 26
11. To compare LY900014 and insulin lispro with respect to the proportion of patients achieving HbA1c targets	11. The proportion of patients with HbA1c <7% and ≤6.5% at Week 26
Tertiary/Exploratory Objectives	
12. To compare the safety of LY900014 and insulin lispro	12. Adverse events, vital signs, chemistry, and hematology laboratory measures
13. To compare the incidence of treatment-emergent positive anti-insulin lispro antibodies for LY900014 and insulin lispro	13. Incidence of treatment-emergent positive anti-insulin lispro antibodies
14. To compare LY900014 and insulin lispro with respect to quality of life as measured by the EQ-5D-5L	14. Change from baseline in EQ-5D-5L UK-population based health state index score and EQ-VAS score at Week 26
15. To compare LY900014 and insulin lispro with respect to diabetes treatment satisfaction as measured by the ITSQ	15. Change from baseline in ITSQ regimen inconvenience and lifestyle flexibility domain scores at Week 26
16. To compare LY900014 and insulin lispro with respect to the impact that diabetes has on the ability to work and perform regular activities as measured by the WPAI-GH	16. Change from baseline in WPAI-GH item scores at Week 26
17. To compare LY900014 and insulin lispro with respect to changes in body weight	17. Change in weight (kg) from baseline to Week 26
18. To compare LY900014 and insulin lispro with respect to glycemic variability	18. Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 10-point SMBG profiles

Objectives and Endpoints

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; EQ-5D-5L = European Quality of Life – 5 Dimensions 5 Level; EQ-VAS = EuroQol visual analogue scale; HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire; MMTT = mixed-meal tolerance test; NIM = noninferiority margin; PPG = postprandial glucose; SMBG = self-monitored blood glucose; T1D = type 1 diabetes mellitus; WPAI-GH = Work Productivity and Activity Impairment General Health.

5. Study Design

5.1. Summary of Study Design

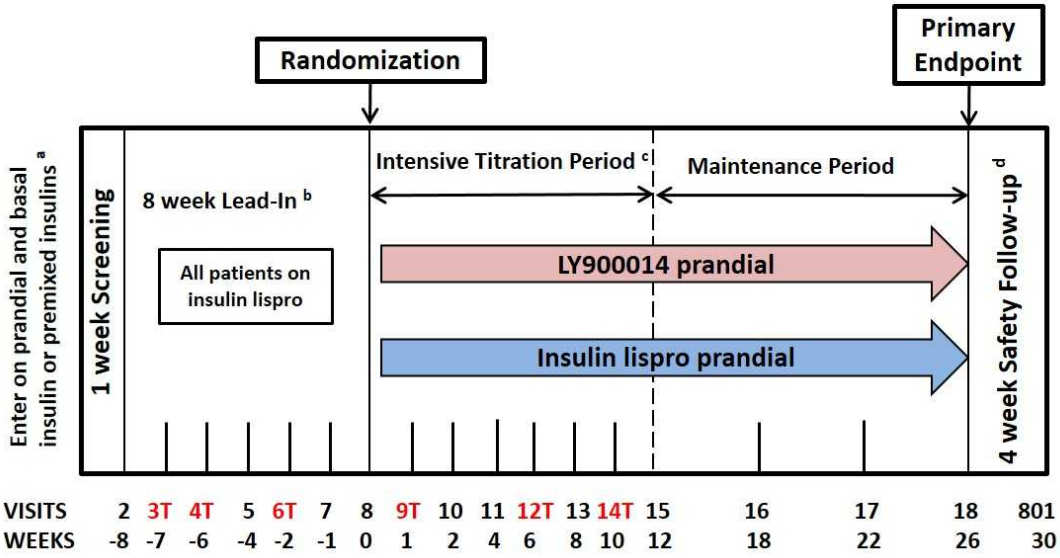
Study I8B-FH-ITSD (ITSD) is a Phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter, parallel, active-controlled study in patients with type 1 diabetes mellitus (T1D) currently using a multiple daily injections regimen. The study includes a 1-week screening period and an 8-week lead-in period followed by a 26-week treatment period and a 4-week safety follow-up period. Figure 5.1 illustrates the study design.

5.2. Determination of Sample Size

Patients will be randomized in a 1:1 ratio to double-blind LY900014 dosed 0 to 2 minutes before meals, or double-blind insulin lispro dosed 0 to 2 minutes before meals. Assuming a noninferiority margin (NIM) of 0.4%, no true difference between treatment arms, and a standard deviation (SD) of 1.1%, approximately 298 completers (149 in each treatment group) will provide 87% power to show noninferiority between LY900014 and insulin lispro in change from baseline to 26 weeks in hemoglobin A1c (HbA1c) using the upper limit of a 2-sided 95% confidence interval (CI; LY900014 – insulin lispro). Assuming a 15% dropout rate for 26 weeks, approximately 350 patients will need to be randomized.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 8. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Patients will be randomized to 1 of the 2 treatment groups in a 1:1 ratio. Stratification will be by country (China vs. Other), HbA1c stratum (≤8.5% vs. >8.5% at Visit 7), type of basal insulin during the lead-in period (glargine U-100 vs. degludec U-100), and use of metformin at study entry (yes vs. no).



Abbreviation: T = telephone visit.

a At Visit 2, patients on insulin glulisine, insulin aspart, regular human insulin, or premixed insulin will be transferred to insulin lispro. The patients' basal insulin regimen will be switched to insulin glargine U-100 once daily or to insulin degludec U-100 once daily. At Visit 8, patients will be randomized to either premeal insulin lispro or premeal LY900014 and continue their basal insulin regimen.

b Titrate basal insulin

c Titrate prandial insulin (insulin lispro or LY900014)

d Patients will discontinue study insulins at Week 26.

Figure 5.1. Illustration of study design.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter 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.

For purposes of analysis, the following populations are defined in Table 6.1.

Table 6.1. Patient Populations

Population	Description
Entered	All patients who give informed consent.
Enrolled	All patients who receive at least 1 dose of open-label insulin lispro in the 8-week lead-in period.
Randomized	All patients who are randomly assigned to study treatment at Visit 8. Treatment group will be defined on the basis of the treatment the patients are assigned.
Safety	All randomized patients who receive at least 1 dose of the randomly assigned investigational product (IP). Treatment group will be defined on the basis of the treatment the patients are assigned.
Completer	Patients included in the randomized population who have completed Week 26 of study treatment without permanent discontinuation of IP. Treatment group will be defined on the basis of the treatment the patients are assigned.
Per Protocol	Patients included in the randomized population who have completed Week 26 of study treatment without permanent discontinuation of IP and without significant protocol deviations through Week 26 that would significantly impact the primary objective. Treatment group will be defined on the basis of the treatment the patients actually receive.

Unless otherwise stated, the efficacy analyses will be conducted on the Randomized Population, and the safety analyses will be conducted on the Safety Population.

The primary analysis is for the treatment period through Week 26.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

The definitions of baseline and postbaseline for the efficacy and safety analyses depend on which analysis period is being used. The following analysis periods will be used:

- Lead-in Period – Visits 2-8
- 26-Week Treatment Period – from randomization to Week 26 prior to discontinuation of IP
- 26-Week Treatment Period and Safety Follow-Up Visit - from randomization to Visit 801 (including all data regardless of IP use)

The data on IP is defined based on the following rules:

- for data only measured at an office visit
    - MMTT postbaseline data will be considered as data on IP if the MMTT performance date is on or prior to the last IP dose date
    - Other postbaseline data (for example, vital signs, laboratory tests, and questionnaires) will be considered as data on IP if the measurement date is on or prior to the cutoff date defined as 14 days after the last IP dose date
- for data collected as running records with an exact date stamp such as adverse events (AEs) and diary entries where the dates of the measures were not tied with the date of an office visit, postbaseline data with dates ≤ (last study drug dose date +1) will be considered as data on IP.

Table 6.2 describes the rules for determining the patient population, baseline and postbaseline observations for the different analysis periods.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-squares (LS) means and standard errors derived from the analysis models will also be displayed. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test will be used for treatment comparisons.

For laboratory values, Systeme International (SI) units will be presented. Therefore, both % and mmol/mol will be presented for HbA1c and mmol/L will be presented for glucose measurements.

All baseline measures will be analyzed using an analysis of variance (ANOVA) model that has treatment as the model terms.

Table 6.2. Baseline and Postbaseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Postbaseline Observations
Lead-In Period			

TEAEs	All Enrolled Patients	Prior to first dose of open-label insulin lispro (or Visit 2 date if the dose date is missing)	The entire lead-in period after first dose of open-label insulin lispro and prior to the first dose of IP (or Visit 8 date if the dose date is missing)
Basal, prandial, and total insulin doses, and prandial/total insulin dose ratio	All Randomized Patients	Visit 2	Visits 3–8 prior to initiation of IP
Weight MMRM and ANCOVA	All Randomized Patients	Last of Visits 1-2	Visits 3–8 AND Last of Visits 3-8
26-Week Treatment Period (including Safety Follow-Up Visit where applicable)			
HbA1c MMRM and ANCOVA	All Randomized Patients with a baseline and at least 1 postbaseline observation while on IP	Last of Visits 7-8	Visits 11, 13, 15, and 18 prior to discontinuation of IP AND Last of Visits 9-18 prior to discontinuation of IP

Baseline and Postbaseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Postbaseline Observations
HbA1c categorical analyses longitudinal logistic regression and LOCF logistic regression	All Randomized Patients with a baseline and at least 1 postbaseline observation while on IP	Last of Visits 7-8	Visits 11, 13, 15, and 18 prior to discontinuation of IP AND Last of Visits 9-18 prior to discontinuation of IP
1-hr and 2-hr PPG and other MMTT variables	All Randomized Patients with a postbaseline observation while on IP	Visit 8 prior to initiation of IP	Visit 18 prior to discontinuation of IP
10-point SMBG, basal, prandial, and total insulin doses, prandial/total insulin dose ratio	All Randomized Patients with a baseline and at least one postbaseline observation	Visit 8 prior to initiation of IP	Visits 15, and 18 prior to discontinuation of IP AND Last of Visits 9 to 18 prior to discontinuation of IP
1,5-AG	All Randomized Patients with a baseline and at least 1 postbaseline observation	Visit 8 prior to initiation of IP	Visits 11, 15, and 18 prior to discontinuation of IP AND Last of Visits 9-18 prior to discontinuation of IP
Health outcomes: ITSQ, EQ-5D-5L, EQ-VAS, WPAI-GH	All Randomized Patients with a baseline and a postbaseline observation	Last of Visits 1-8	Last of Visits 9-18 prior to discontinuation of IP
Safety Laboratory Tests (chemistry, hematology, lipids) – continuous analysis	All Patients in the Safety Population with a baseline and a postbaseline observation	Last of Visits 1-8	Visit 18 (planned) AND Last of Visits 9-18 (planned including early discontinuation visits), regardless of IP use
Safety Laboratory Tests (chemistry, hematology, lipids) – categorical analysis	All Patients in the Safety Population with a normal baseline (with respect to the direction being analyzed) and a postbaseline observation	Visits 1 -8 (including unplanned tests)	Visits 9-18 (including unplanned tests), regardless of IP use

Baseline and Postbaseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Postbaseline Observations
TEAEs	All patients in the Safety Population	Prior to first dose of randomized IP (or Visit 8 date if missing) and after the first dose of open-label insulin lispro (or Visit 2 date if missing)	From first dose of randomized IP to last dose of randomized IP AND From first dose of randomized IP to Visit 801
Hypoglycemia events	All patients in the Safety Population	All Visits 2-8	All Visits 9-18 prior to discontinuation of IP
Weight and vital signs	All Patients in the Safety Population with a baseline and a postbaseline observation	Last of Visits 2-8	Visits 9-18 prior to discontinuation of IP AND Visits 9-801 regardless of IP use
Anti-insulin lispro antibody	Safety Population	Visit 2	Visits 3-801 regardless of IP use

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; ANCOVA = analysis of covariance; EQ-5D-5L = European Quality of Life– 5 Dimensions 5 Level; EQ-VAS = EuroQol visual analogue scale; HbA1c = hemoglobin A1c; IP = investigational product; ITSQ = Insulin Treatment Satisfaction Questionnaire; ITT = intention-to-treat; LOCF = last-observation-carried forward; MMTT = mixed meal tolerance test; MMRM = mixed-effect model repeated measures; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event; WPAI-GH = Work Productivity and Activity Impairment General Health.

6.2. Adjustments for Covariates

Stratification will be by country (China vs. Other), HbA1c stratum (≤8.5% vs. >8.5% at baseline), type of basal insulin during the lead-in period (glargine U-100 vs. degludec U-100), and use of metformin at study entry (yes vs. no). Stratification factors will be entered into the IWRS for randomization and also collected in the database by electronic case report form (eCRF) or central laboratory. The analysis models for efficacy endpoints will use the stratification factors as collected in the database.

For continuous analyses of HbA1c, the stratification factor of HbA1c stratum (baseline) will not be included. Instead, the continuous value of baseline HbA1c will be included in the analysis models.

Other analyses will include the stratification factors as noted in Sections 6.11 and 6.12.

6.3. Handling of Dropouts or Missing Data

The analyses for the primary and multiplicity adjusted objectives will be performed on data collected prior to discontinuation of IP through Week 26.

Missing data will be addressed by using a mixed-effect model repeated measures (MMRM) analysis for continuous longitudinal variables. The MMRM model provides consistent estimator when data is missing at random. The model implicitly adjusts for missing data through a variance-covariance structure. An ANCOVA model will also be used to analyze continuous variables.

Unless otherwise stated, missing endpoints will be imputed using the last-observation–carried forward (LOCF) approach, using only postbaseline data, in the ANCOVA model.

6.4. Multicenter Studies

I8B-MC-ITSD is a multi-country, multi-site study. Site will not be analysed as a fixed effect in any of the models so pooling strategies will not be required.
China level reports of selected enrollment, baseline, efficacy and safety data may also be produced, as applicable.

Summary results for Argentina and Mexico may produced per country specific regulatory requirement.

6.5. Multiple Comparisons/Multiplicity

A graphical approach for multiple comparisons will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the multiplicity adjusted objectives given in Section 4. See Section 6.11.2 for the details of graphical testing scheme.

No multiplicity test adjustment will be made for other objectives.

6.6. Patient Disposition

Frequency counts and percentages of all randomized patients completing and discontinuing from the study and study treatment will be presented for each treatment group. Reasons for discontinuation from the study and study treatment during the 26-week treatment period will be compared between treatment groups using Fisher's exact test. Reasons for discontinuation from the study at Visit 801 will be summarized by the randomized treatment groups.

Frequency counts and percentages of all entered patients, enrolled, and discontinuing from the study during the lead-in period will be summarized. Reasons for discontinuation during screening will be summarized for all entered patients. Reasons for discontinuation from the study during the lead-in period will be summarized for all enrolled patients.

Time to all-cause discontinuation (discontinuation for any reason) from the study and from study treatment will be compared between treatment groups for the 26-week Treatment Period. The Kaplan-Meier product limit method will be used to create survival curves and the log-rank test will be used for the treatment comparisons. Time to all-cause discontinuation is defined as the total number of days between the randomization date (Visit 8 date) and date of discontinuation plus 1. Patients who complete the treatment period will be treated as censored using the total number of days between the randomization date and the Visit 18 date plus 1. If sufficient numbers of patients discontinue the study because of an AE, similar analysis will be performed for time to discontinuation due to an AE.

A listing of the primary reason for treatment discontinuation (if applicable) and study discontinuation will be generated for the Enrolled Population.

Patient allocation by investigator, grouped by country, will be summarized indicating the number of patients who enter the study, the number of patients who participate in the lead-in period, the number of patients who are randomized to study treatment, and the number of patients who discontinue the study.

A listing of the randomization treatment assignment will be generated for all randomized patients.

A listing with all the entered subjects indicating entered, enrolled, randomized, safety, completer of treatment, completer of study, per protocol will be provided.

6.7. Patient Characteristics

A summary table will be generated for patient characteristics at study entry using all randomized patients. The following variables will be included but not limited to: age, age groups (<40 and ≥40 years and 18 to 64, and ≥65 years), sex, country, race, height, weight, body mass index (BMI), BMI groups (<25, ≥25 to <30, ≥30 kg/m^2). For continuous variables, the following statistics will be provided: mean, SD, minimum, maximum, and median, and treatment groups will be compared using an ANOVA model with a term of treatment. For categorical variables, summary statistics will include sample size, frequency and percentage, and treatment groups will be compared using Fisher's exact test or Pearson's chi-square test. A listing of patient characteristics at study entry will be provided.

A similar summary of diabetes characteristics will also be generated. The following variables will be included but not limited to: duration of diabetes, the type of prandial insulin at study entry (that is, screening), use of metformin at study entry, the type of basal insulin therapy at study entry (including whether given once daily [QD] or twice-daily [BID]) and during lead-in, prandial insulin dosing plan, HbA1c at study entry and baseline, HbA1c stratum at baseline, and fasting serum glucose at Visit 2 and baseline (based on MMTT).

A listing of patients whose stratification factor value entered into the IWRS (for treatment group assignment) is different from the clinical database will also be provided.

For all randomized patients, the number and percentage of patients with historical conditions will be summarized by treatment group using Medical Dictionary for Regulatory Activities (MedDRA) PT (without regard to SOC), and the number and percentage of patients with preexisting conditions will also be summarized by treatment group using MedDRA PT (without regard to SOC). Historical conditions are conditions that end prior to inform consent and preexisting conditions are conditions that are still ongoing at inform consent. Events will be ordered by decreasing frequency. No statistical comparisons between treatment groups will be performed.

6.8. Treatment Compliance

No analysis for treatment compliance is planned for this study.

6.9. Important Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations are

defined as those deviations from the protocol likely to have a significant impact on the

completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

CCI

The listing of important protocol deviations for all randomized patients during the entire study, with the indication of whether to be excluded from the PP population, will also be provided. CCI

6.10. Concomitant and Prior Therapy

Concomitant medication and pre-study insulin treatment type will be summarized and compared between treatment groups using Fisher's exact test (or Chi-Square test) for the Randomized Population during the treatment period. The percentages of patients receiving each concomitant medication will be summarized by treatment using PT nested within Anatomical Therapeutic Chemical (ATC) Level 3 code. Medications will be ordered by decreasing frequency within ATC level. Concomitant medication used during the lead-in period will also be summarized for the Enrolled Population.

A summary of previous diabetes therapies that were discontinued prior to informed consent will be generated for the Enrolled Population.

At a given visit, total daily basal insulin dose to be used for analysis will be calculated as the mean of the total daily basal insulin doses on the 3 days prior to the visit date (or the days between the previous visit date and the current visit date if the number of days between the 2 visit dates is <3). Similarly, the dose for each meal will be calculated as the mean of the doses on the 3 days prior to the visit date (or the days between the previous visit date and the current visit date, whichever smaller). Total daily prandial insulin dose to be used for analysis will be calculated as the sum of the individual meal insulin doses. If either total daily basal insulin dose or total daily prandial insulin dose is missing, total daily insulin dose and prandial/total insulin dose ratio will be set as missing for analysis.

The total daily basal insulin dose, total daily prandial insulin dose, total insulin dose, and the ratio of prandial insulin dose to total insulin dose during the lead-in period will be summarized by visit for the Randomized Population. The actual and change from Visit 2 values will be compared between treatment groups using an MMRM model including the corresponding dose at Visit 2, treatment, strata (country, type of basal insulin, use of metformin at study entry and HbA1c stratum), visit, treatment-by-visit interaction in the model as fixed factors and patient as a random factor. Doses will be summarized in U and U/kg. Basal insulin dose will be summarized independently for glargine and degludec as well as combined.

6.11. Efficacy Analyses

6.11.1. Primary Outcome and Methodology

The primary objective of this study (H1) is to test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control (NIM=0.4% for HbA1c) in patients with T1D, when administered as prandial insulin (0-2 minutes prior to the meal), in combination with basal insulin for 26 weeks.

The primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro at Week 26 (Visit 18) from the MMRM analysis of change from baseline in HbA1c including data collected from all randomized patients prior to discontinuation of IP through Week 26. The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment, strata (country, type of basal insulin, use of metformin at study entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on LS means and Type III tests. If this analysis fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- autoregressive with heterogeneity
- compound symmetry with heterogeneous variances
- Toeplitz
- autoregressive
- compound symmetry without heterogeneous variances

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

LY900014 will be declared noninferior to insulin lispro if the upper limit of the 2-sided 95% CI for the LS mean difference in the change from baseline in HbA1c for LY900014 minus insulin lispro is below +0.4%.

6.11.2. Analyses of Multiplicity Adjusted Objectives

A graphical approach for multiple comparisons (Bretz et al. 2011) will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the following multiplicity adjusted objectives: superiority of LY900014 compared with insulin lispro for (H2) 1-hour postprandial plasma glucose (PPG) excursion at the study primary endpoint, (H3) 2-hour PPG excursion at the study primary endpoint, and (H4) change from baseline to the study primary endpoint in HbA1c.

The graphical testing scheme for this study is displayed in Figure 6.1. All the hypotheses are connected by lines with arrowheads indicating the directions of testing paths. The initial allocation of study total alpha for each hypothesis is located within the same node of the hypothesis. In this

study, the study total alpha level (0.05) will be all used for the primary objective (H1) in the initial step. In this study, the study total alpha level (0.05) will be all used for the primary objective (H1) in the initial step. Then, the study total alpha level (0.05) will be allocated to other objectives according to the values of transition weights shown above the connecting lines in the figure once H1 is met. If 1 of the remaining objectives is successfully demonstrated with the given alpha level, its alpha will be allocated to the rest of objectives by the transition weights in the paths. The iterative test procedure continues until none of the remaining objectives can be demonstrated with their preserved alphas or all objectives are demonstrated successful.

An ANCOVA model with strata (country, type of basal insulin, use of metformin at study entry and HbA1c stratum) and treatment as fixed effects and baseline as a covariate will be used to analyze the 1-hour and 2-hour PPG excursions for data collected prior to discontinuation of IP. However, if the percentage of the patients with missing MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead.

The superiority testing on change from baseline to the study primary endpoint in HbA1c will be assessed by the same analysis used for the primary objective. If the p-value is less than the alpha level allocated by the graphical approach, the superiority of LY900014 to insulin lispro will be achieved.

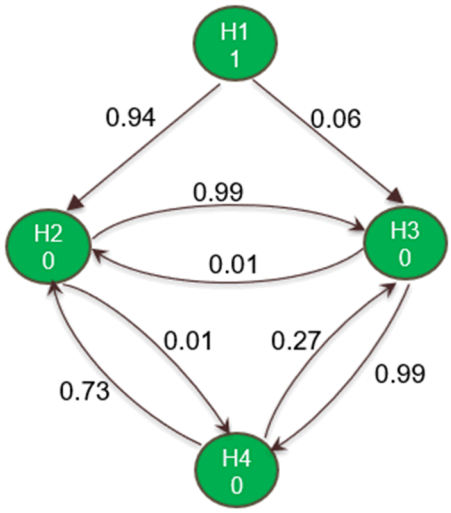


Figure 6.1. Testing scheme for primary and multiplicity adjusted objectives.

6.11.3. Additional Analyses of the Primary Outcome

The primary MMRM analysis model will be repeated using the PP and Completer populations as a sensitivity analysis. If the conclusion differs from that of all randomized patients, the data and analyses will be further investigated.

A secondary analysis model will be an ANCOVA for HbA1c change from baseline to the study primary endpoint, using the model with strata (country, type of basal insulin, use of metformin at study entry) and treatment as fixed effects and baseline as a covariate. Missing endpoints will be imputed using the LOCF approach using postbaseline data only.

6.11.4. Sensitivity Analyses for Missing Data

There is no sensitivity analyses for missing data.

6.11.5. Other Secondary Efficacy Analyses

The longitudinal observations of actual and change from baseline in HbA1c up to Week 26 will be analyzed using the same MMRM model as for the analysis of the primary outcome. For the following secondary efficacy endpoints, an MMRM model similar to that for the primary outcome with an additional term of HbA1c stratum (≤8.5%, >8.5%) will be used:

- actual and change from baseline 1,5-AG values
- actual and change from baseline 10-point SMBG values (fasting, 1 hour post morning meal, 2 hours post morning meal, pre midday meal, 1 hour post midday meal, 2 hours post midday meal, pre evening meal, 1 hour post evening meal, 2 hours post evening meal, and bedtime)
- actual and change from baseline in total, basal, and prandial insulin doses and prandial/total insulin dose ratios

Three 10-point SMBG profiles are expected to be collected during the 2 weeks prior to specified visits. Valid SMBG profiles will be used for analysis, defined as having non-missing values at ≥6 time points among the 10 pre-specified time points and being collected 2 weeks prior to the given visit. For each time point, the average of the corresponding SMBG values from the valid SMBG profiles will be used for analysis. The excursion of SMBG for each meal category (that is, morning meal, midday meal, and evening meal) calculated using the average values at the corresponding time points will be used for analysis.

The following endpoints, collected from the MMTT, will be analyzed using the ANCOVA model with strata (country, type of basal insulin, use of metformin at study entry and HbA1c stratum) and treatment as fixed effects and baseline as a covariate:

- actual and change from baseline in fasting glucose (average of measurements at time -15 and 0), and PPG at 15, 30, 60, 120, 180, and 240 minutes after the meal
- PPG excursions at time 15, 30, 180, and 240 minutes after the meal (PPG minus fasting glucose)

Sensitivity analysis for PPG excursions may be performed to exclude patients whose PPG excursion could be affected by factors including MMTT consumption amount (for example, partial MMTT was consumed) and correction bolus insulin usage. A summary of the MMTT consumption and bolus insulin dose at baseline and Week 26 will be provided.

Treatment comparisons for the proportion of patients with HbA1c <7.0% and ≤6.5% will be analyzed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c-by-visit interaction, and treatment-by-visit interaction. An unstructured covariance structure will be used. As a sensitivity analysis, the proportion of patients

with HbA1c <7.0% and ≤6.5% at Week 26 (Visit 18), imputed using LOCF, will be compared using a logistic regression model with terms for treatment and baseline HbA1c value.

6.11.6. Secondary Health Outcomes Analyses

For the Insulin Treatment Satisfaction Questionnaire (ITSQ), the change from baseline to LOCF endpoint while on treatment in each domain transformed score (inconvenience, lifestyle, hypoglycemic control, glycemic control, delivery system) and overall transformed score will be analyzed using the ANCOVA model with strata (country, type of basal insulin, use of metformin at study entry and HbA1c stratum), and treatment as fixed effects and baseline as a covariate.

6.11.7. Analyses of Exploratory Objectives

Summary statistics, including number of patients and proportion of categorical outcomes (5 levels) for the 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) of the European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L) will be provided by visit and by treatment. The change from baseline to LOCF endpoint (Week 26, Visit 18) in the EQ-5D-5L United Kingdom (UK) population-based health state index score and EuroQol visual analogue scale (EQ-VAS) score will be analyzed using the ANCOVA model CCI [redacted]

For the Work Productivity and Activity Impairment General Health (WPAI-GH), the change from baseline to LOCF endpoint in each score (absenteeism, presenteeism, work productivity loss, and activity impairment) will be analyzed using the ANCOVA model similar to ITSQ.

Within-day and between-day glycemic variability measured by the standard deviation (SD) and the coefficient of variation (CV) of 10-point SMBG profiles will also be analyzed by MMRM model specified in Section 6.11.5. At a given visit, the CV and SD on each day with a valid SMBG profile will be calculated using all the glucose values within that day, then the average values of these CVs and SDs will be used as the within-day CV and SD at that visit in analysis. At a given visit, the CV and SD at each of the 10 pre-specified SMBG time points will be calculated using the corresponding glucose values of the valid SMBG profiles, then the average values of these CVs and SDs will be used as the between-day CV and SD at that visit in analysis.

Table 6.3. lists additional variables for potential exploratory analyses.

Table 6.3. Additional Exploratory Efficacy Variables

Variable Description	Derivation	Statistical Method
Incremental areas under the serum glucose concentration-time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after the meal in MMTT.	iAUC+: the total area under the serum glucose curve but above the glucose level at time 0 when the meal starts for the MMTT within the specific time frame. The area will be calculated by trapezoids rule.	ANCOVA
Area under/above the serum glucose concentration time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after the meal in MMTT.	• AUC: Total area under the serum glucose curve calculated by trapezoids area within the specific time frame	ANCOVA

	• $AUC_{>180}$: Total area under the serum glucose curve but above the 18 0mg/dL level within the specific time frame • $AOC_{\leq 70}$: Total area above the serum glucose curve but below the 70 mg/dL level within the specific time frame.	
Glucose variability during MMTT	• The CV of all serum glucose values collected during the MMTT • The SD of all serum glucose values collected during the MMTT.	ANCOVA
1-hour and 2-hour PPG excursions and daily mean by 10-point SMBG profile	• The difference in means between 1-hour PPG and fasting PG at the same visit • The difference in means between 2-hour PPG and fasting PG at the same visit • The average of daily means at the same visit	MMRM
Incidence of HbA1c ≤6.5% and <7.0% without severe hypoglycemia	• Binary indicator with 1 indicating HbA1c ≤6.5% at Week 26 and no severe hypoglycemia during 0-26 weeks of treatment • Binary indicator with 1 indicating HbA1c <7% at Week 26 and no severe hypoglycemia during 0-26 weeks of treatment.	Logistic regression

Abbreviations: ANCOVA = analysis of covariance; AOC = area over the curve; AUC = area under the curve; CV = coefficient of variation; iAUC = incremental area under the curve; HbA1c = hemoglobin A1c; MMRM = mixed-meal tolerance test; MMTT = mixed-meal tolerance test; PG = plasma glucose; PPG = postprandial glucose; SD = standard deviation; SMBG = self-monitored blood glucose.

6.12. Safety Analyses

Safety measures will include AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro. Refer to Table 6.1 and Table 6.2 for the analysis population and the baseline definition used in the analysis of a safety measurement for a specific study period.

6.12.1. Extent of Exposure

Duration of exposure to IP will be summarized. The following summary statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (that is, total patient-years of exposure). The number and proportion of patients falling into the following different exposure categories will also be summarized: <1 month (>0 and <30 days), ≥1 and <3 months (≥30 and <90 days), ≥3 and <6 months (≥90 days and <180 days) and ≥6 months (≥180 days).

Patients who complete the study treatment period are required to complete a safety follow-up visit without study drug; and patients who discontinue the IP prematurely are encouraged to remain in the study without study drug. The days on study after discontinuing IP, and the days on study from date of first study drug to the last study visit date up to Visit 801 will also be summarized.

6.12.2. Adverse Events

Analyses of AEs will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data prior to discontinuation of IP. The second set of analyses will include all data in the corresponding analysis period regardless of IP use.

Events that are newly reported after the first dose of prandial insulin provided as study drug (that is, open-label insulin lispro used during the lead-in period or IP used during the treatment period) or reported to worsen in severity from baseline (defined in Table 6.2) will be considered TEAEs. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity. For events occurring on the day of first dose of bolus insulin provided by this study, the case report form (CRF)-collected flag will be used to determine whether the event started or worsened post-treatment.

In an overview table, the number and percentage of patients who experienced a TEAE, experienced a serious adverse event (SAE), died due to an AE, discontinued from study due to an AE, or discontinued IP due to an AE will be summarized by treatment group.

The number and percentage of patients with TEAEs will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. As an additional table, the percentages of patients with TEAEs will be summarized by treatment using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency. Statistical comparisons will be applied at both the SOC and PT levels. Fisher's exact test will be performed for treatment comparison.

The number and percentage of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT (without regard to SOC) and data collected prior to discontinuation of IP. For each patient and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. No statistical comparison between treatment groups will be conducted.

The number and percentage of patients with common TEAEs (defined as ≥5% before rounding in LY900014-treated patients) will be summarized by treatment group using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency. Treatment will be compared by Fisher's exact test.

The number and percentage of patients who experienced an SAE, including deaths and SAEs temporally associated or preceding deaths, will be summarized by treatment group using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency. A listing of all SAEs will also be provided.

The number and percentage of patients who discontinued from study due to an AE will be summarized by treatment group using MedDRA (without regard to SOC) using all data regardless of IP use. The number and percentage of patients who discontinued IP due to an AE will be also summarized by treatment group using MedDRA PT (without regard to SOC) using data prior to

discontinuation of IP. Events will be ordered by decreasing frequency. A listing of all AEs as reason for study or IP discontinuation will also be provided.

The number and percentage of patients who experienced other notable TEAEs (potential systemic hypersensitivity reaction, injection site reaction, and hepatic disorder) will be summarized by treatment group using all TEAEs regardless of IP use.

For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

Table 6.4 summarizes the planned analyses and the requirement of analysis data for different analysis periods. A 'Yes' in the IP USE column indicates that only data collected prior to discontinuation of IP will be included.

Table 6.4. Treatment-Emergent Adverse Event Analysis Periods

Analysis Period	Analysis Population	Analysis	IP USE	Treatment
Lead-in Period	All enrolled patients	AE overview; TEAE by PT, SAE, discontinuation from study due to AE	N/A	Open-label insulin lispro
Treatment Period (0-26 Weeks)	All patients in safety population	AE overview; TEAE by SOC and by PT; common TEAE; TEAEs by maximum severity; SAE; discontinuation from IP due to AE	Yes	LY900014, insulin lispro,
Week 0 – Visit 801	All patients in safety population	AE overview; TEAE by SOC; common TEAE; SAE; other notable AEs; study discontinuation due to AE	All data regardless of IP use	LY900014, insulin lispro

Abbreviations: AE = adverse event; IP = investigational product; N/A = not applicable/available; PT = Preferred Term; SAE = Serious Adverse Event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

6.12.3. Deaths

The listing of all deaths by patient for all enrolled patients will be provided as part of the SAE listing, regardless of the investigator's or the sponsor's judgment about causality. Each listing will include study ID, investigator ID, patient ID, treatment group, baseline age, sex, associated AE, first and last dose date for open label insulin lispro and randomized IP, and the event date.

6.12.4. Hypoglycemic Events and Other Adverse Events

The analysis plans for the following adverse events are discussed in Section 6.12.4.1 through Section 6.12.4.4:

- hypoglycemic events
- systemic hypersensitivity reaction
- injection site reaction
- hepatobiliary events

These AE analyses will be similar to the TEAE analyses. Refer to Table 6.4 for the requirement of analysis data for a specific analysis period.

6.12.4.1. Hypoglycemic Events

Hypoglycemia events that occur during the study outside the MMTT will be captured starting from Visit 2 through Visit 801. Whenever hypoglycemia is suspected, the patient should record the blood glucose value, any associated symptoms, and the treatment administered in patient diary. A set of events is counted as 1 event in analysis if it consists of an originating event and subsequent continuing events as marked by the patient in paper diary, or the duration between adjacent events

is ≤30 minutes. The event with the highest severity will be selected for analysis with severity determined in the order of: 1) it is a severe hypoglycemia, 2) it has symptoms of hypoglycemia reported, and 3) it has the lowest blood glucose value. If there are multiple events tied in all 3 aspects, the event with the largest number of non-missing responses to the questions of nocturnal hypoglycemia and postmeal time frame will be selected. If there are still multiple events tied, the latest event (based on data entry time) will be selected.

The following types of hypoglycemia events will be derived in the analysis data sets: documented hypoglycemia, severe hypoglycemia, nocturnal hypoglycemia (documented and occurring between bedtime and waking), probable symptomatic hypoglycemia, and overall hypoglycemia. Only severe hypoglycemia will be collected as AEs and all episodes of severe hypoglycemia will be considered as SAEs. Documented hypoglycemia (including documented symptomatic hypoglycemia, documented asymptomatic hypoglycemia and documented unspecified hypoglycemia) will be based on blood glucose (BG) ≤70 mg/dL. In addition, documented clinically significant hypoglycemia with similar criterion as above documented hypoglycemia except for the threshold of BG <54 mg/dL will be summarized.

Table 6.5 provides detailed statistical methods for each endpoint related to hypoglycemia. For these analyses, hypoglycemia events prior to discontinuation of IP will be summarized. Additional analyses for other types of hypoglycemic events not mentioned in the table and for the post-treatment period may be conducted as needed.

The incidence and number of episodes of hypoglycemia (regardless of the type of hypoglycemia event) during the MMTT will be summarized by treatment and time relative to the meal (≤0.5, ≤1, ≤2, ≤4, >1 to ≤2 and >2 to ≤4 hours after start of the meal) and analyzed by Fisher's exact test.

A listing of patients with at least 1 severe hypoglycemia reported (as SAE) after randomization will be provided. Summary of severe hypoglycemia treatment and outcome from the patient diary will be provided.

A list of MedDRA PTs will be used for the narrow search of potential severe hypoglycemia in spontaneously reported AEs. The events identified through the search strategy that are also reported as SAEs will be summarized and compared between treatments. Fisher's exact test will be used to assess the treatment difference in the proportion of patients with potential severe hypoglycemia.

Table 6.5. Summary of Analyses for Endpoints Related to Hypoglycemia

Endpoint	Analysis Period	Statistical Method
Rate of hypoglycemic events (per patient per 30 days / year) All Documented[a] Nocturnal[a] Documented Symptomatic[a] Non-Nocturnal (or Daytime) (Documented and between waking and bedtime)[a]	0-12, 0-26, 12-26weeks	Negative binomial regression with treatment, and log (exposure/30 days for exposure/365.25 days) as the offset in the model.

Endpoint	Analysis Period	Statistical Method
Incidence of hypoglycemic events All Documented[a] Nocturnal[a] Documented Symptomatic[a] Non-Nocturnal (or Daytime) (Documented and between waking and bedtime)[a]	0-12, 0-26, 12-26 weeks	Logistic regression with treatment as an independent variable.
Rate of postmeal hypoglycemic events (per patient per 30 days / year) for all 3 main meals Documented Symptomatic[a]	≤0.5, ≤1, ≤2, ≤4, >1 to ≤2 , >2 to ≤4 and >4 hours after start of a meal within 0-12, 12-26, 0-26 weeks	Negative binomial regression with treatment, and log (exposure/30 days or exposure/365.25 days) as the offset in the model.
Incidence of postmeal hypoglycemic events for all 3 main meals Documented Symptomatic[a]	≤0.5, ≤1, ≤2, ≤4, >1 to ≤2, >2 to ≤4 and >4 hours after start of a meal within 0-12,12-26, 0-26 weeks	Logistic regression with treatment as an independent variable.
Rate of severe hypoglycemic events (per patient per year / 100 years)	0-12, 0-26, 12-26 weeks	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 0 for details) will be used for treatment comparison.

Summary of Analyses for Endpoints Related to Hypoglycemia

Endpoint	Analysis Period	Statistical Method
Incidence of severe hypoglycemic events	0-12, 0-26, 12-26 weeks	Proportion of patients with severe hypoglycemia will be reported. The treatment comparison will be based on a logistic regression model with treatment as an independent variable.
Rate of postmeal severe hypoglycemic events (per patient per year / 100 years) for all 3 main meals	≤0.5, ≤1, ≤2, ≤4, >1 to ≤2 , >2 to ≤4 and >4 hours after start of a meal within 0-12,12-26, 0-26 weeks	Due to limit data for the rare event, only summary statistics will be provided by treatment. No statistical comparison will be conducted.
Incidence of postmeal severe hypoglycemic events for all 3 main meals	≤0.5, ≤1, ≤2, ≤4, >1 to ≤2 , >2 to ≤4 and >4 hours after start of a meal within 0-12, 12-26, 0-26weeks	Fisher exact test will be used for treatment comparison.

[a] All documented hypoglycemia and the subcategories based on the thresholds of blood glucose ≤70 mg/dL and blood glucose <54 mg/dL will be analyzed, all postmeal hypoglycemia based on the threshold of ≤70 mg/dL and <54 mg/dL will be applied.

6.12.4.2. Systemic Hypersensitivity Reaction

The number and proportion of patients experiencing treatment-emergent potential systemic hypersensitivity reactions will be summarized and compared by treatment group using Fisher's exact test. The following Standardised 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 (that is, combined search across narrow and algorithmic portions of all 3 SMQs); (2) any narrow scope term within each SMQ, separately (that is, narrow SMQ search); (3) any term within each SMQ, separately (that is, broad SMQ search); (4) narrow scope term search within each SMQ, report the PT nested within each SMQ.

A similar summary will be provided using the TEAEs reported by the investigator as possibly related to study drug.

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.

6.12.4.3. Injection Site Reaction

The injection site reactions will be searched by MedDRA PTs from all TEAEs. The number and percentage of patients experiencing treatment-emergent injection site reaction will be summarized and compared by treatment group using Fisher's exact test.

For injection site reactions, the presence and severity of erythema, induration, pain, pruritus, and edema were collected through the eCRF, and will be summarized for each treatment. There will be no statistical comparison between treatments.

6.12.4.4. Hepatobiliary Events

6.12.4.4.1. Treatment-Emergent Potential Hepatic Disorder

The percentages of patients with treatment-emergent drug-related hepatic disorder events will be summarized and compared 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 potential hepatic disorders:

- 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)

The percentage of patients with any 1 of the terms will be summarized in addition to the percentages for each MedDRA PT. The percentages of patients with potentially drug-related hepatic disorders that led to permanent study treatment discontinuation will be summarized similarly.

6.12.4.4.2. Liver Enzyme and Bilirubin Lab Values

The liver enzyme measures (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], direct bilirubin, total bilirubin) will be summarized by treatment group. Postbaseline value and the change from baseline (last nonmissing value before randomization) to postbaseline value at Week 26 visit (planned tests) will be summarized for patients who have both a baseline and at least 1 postbaseline result, and compared between treatment groups by using ANCOVA model with the term of treatment and baseline value of the response variable. All analyses will be provided in SI units.

The last nonmissing observation at or prior to Week 26 (including early discontinuation visit) will also be analyzed by an ANCOVA model with the term of treatment, baseline value of response variable.

6.12.4.4.3. Treatment-Emergent Elevation of Liver Enzyme Lab Values

The percentages of patients with the following elevations in hepatic laboratory tests at any time during the treatment period (0 to 26) will be summarized between treatment groups:

- The percentages of patients with postbaseline ALT measurement ≥3 times (3X), 5 times (5X), and 10 times (10X) the Covance upper limit of normal (ULN) will be summarized for all patients with a postbaseline value by the following baseline categories: ≤1X, >1X to <3X, ≥3X, missing.
- The percentages of patients with postbaseline AST measurement ≥3 times (3X), 5 times (5X), and 10 times (10X) the Covance ULN will be summarized for all patients with a postbaseline value by the following baseline categories: ≤1X, >1X to <3X, ≥3X, missing.
- The percentages of patients with postbaseline total bilirubin measurement ≥2 times (2X) the Covance ULN will be summarized for all patients with a postbaseline value by the following baseline categories: ≤1X, >1X to <2X, ≥2X, missing.

Baseline will be the maximum observation in the baseline period including the lead-in period. The maximum value will be the maximum value from the treatment period. Planned and unplanned tests will be included.

Graphical profiles of ALT, AST, total bilirubin, and ALP will be provided for patients with an ALT or AST ≥3X ULN or total bilirubin ≥2X ULN during the treatment period. A listing for these patients will also be provided, including the actual measurement of ALT, AST, ALP, and total bilirubin, the corresponding reference high limits, demographics, disposition, drug exposure and AEs. The review for these patients includes an assessment of the proximity of any ALT or AST elevation to any total bilirubin elevation, ALP levels, other potential causes, and the temporal association with events such as nausea, vomiting, anorexia, abdominal pain, or fatigue.

All patient data, regardless of whether on IP, will be used for the above analyses related to hepatobiliary events.

6.12.5. Clinical Laboratory Evaluation

The data from safety laboratory measures will be summarized at Week 26 where the lab test is planned to be collected. Postbaseline and change from baseline to postbaseline for laboratory tests will be summarized for patients who have both baseline and at least 1 postbaseline result and compared between treatment groups by using ANCOVA model with the term of treatment and baseline value of the response variable. Analyses will be provided in SI units.

The last nonmissing observation at or prior to Week 26 (planned tests including early discontinuation) will also be analyzed by an ANCOVA model with the term of treatment, baseline value of the response variable.

The percentages of patients with treatment-emergent abnormal, high, or low laboratory results at any time during the treatment period (0 to 26) will be summarized for patients who have both baseline and at least 1 postbaseline result and compared between treatment groups using Fisher's exact tests. A treatment-emergent abnormal result is defined as a change from normal at all

baseline visits to abnormal at any time during the treatment period. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time during the treatment period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time during the treatment period. Planned and unplanned measurements will be included. CCI be used to define the low and high limits. Only patients who have normal baseline values for the analysis being performed will be included in the analysis for treatment-emergence.

Liver enzymes measures will not be included in the above analyses as different analyses will be used as described in Section 6.12.4.4.2 and Section 6.12.4.4.3.

6.12.6. Vital Signs and Other Physical Findings

Postbaseline measurements and change from baseline to postbaseline for vital signs and physical characteristics (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, weight, BMI) at the scheduled visits will be summarized for patients who have both baseline and at least 1 postbaseline result.

The measurements during the treatment period (0 to 26) will be analyzed by an MMRM model with treatment, baseline value of the response variable, visit, and visit by treatment interaction as fixed factors and patient as the random factor.

Weight during the lead-in period will also be analyzed by an MMRM model with Visit 2 value of the response variable, randomized treatment, visit, and treatment-by-visit interaction as fixed factors and patient as the random factor in all randomized patients.

An ANCOVA model will also be used for the analysis of the last nonmissing observation (including early discontinuation) during the treatment period and during the entire study (up to Visit 801). The ANCOVA models are the same as those used for clinical laboratory measures.

The percentages of patients with treatment-emergent high or low vital signs and weight at any time during the treatment period (0 to 26) or during the entire study including safety follow-up period will be summarized by treatment group for patients who have both baseline and at least 1 postbaseline measurement. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time that meets the specified change criteria during the treatment period or during the entire study including safety follow-up period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time that meets the specified change criteria during the treatment period or during the entire study including safety follow-up period. Treatment comparison will be based on Fisher's exact test. Table 6.6 will be used to define the low and high limits and change thresholds.

Table 6.6. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤60 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<60 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg) (Consistent clothing and timing in relationship to meals and voiding)	(Loss) decrease ≥7%	(Gain) increase ≥7%

Abbreviations: BP = blood pressure.

6.12.7. Immunogenicity

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro for all enrolled patients since Visit 2 prior to the first dose of study-provided prandial insulin treatment. Therefore, the blood sample result at Visit 2 will be considered as the anti-insulin lispro level at baseline for this study.

6.12.7.1. Treatment Emergent Anti-Insulin Lispro Antibody

The treatment-emergent anti-insulin lispro antibody (denoted as treatment-emergent antidrug antibody [TEADA] throughout this SAP) is based on the change from baseline (Visit 2) to postbaseline (post-Visit 2) in the anti-insulin lispro antibody level (percent binding). Treatment-emergent antidrug antibody can be sub-classified as either treatment-induced (not detected anti-insulin lispro antibody at baseline) or treatment-boosted (detected anti-insulin antibody at baseline):

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The TEADA status during a specific analysis period will be determined using all data in the corresponding analysis period regardless of IP use. The summary for TEADA status and the anti-insulin lispro antibody level will use the same analysis data.

The number and percentage of patients with positive TEADA response during the analysis period of Visit 2 to Visit 801 will be summarized by treatment group. For patients with positive TEADA response anytime during the analysis period, the number and percentage of patients with positive

insulin cross-reactivity anytime during the analysis period, and the number and percentage of patients not meeting the TEADA criteria at Visit 801 will also be summarized by treatment group. Treatment groups will be compared by Fisher's exact test.

Both actual and change from baseline (Visit 2) for the anti-insulin lispro antibody level in percent binding will be summarized by scheduled visit prespecified in the protocol for patients with positive TEADA response from Visit 2 to Visit 801. The repeated measurement from Visit 2 to Visit 801 will be analyzed by an MMRM model with treatment, baseline value of the response variable, visit, and visit by treatment interaction as fixed factors and patient as the random factor. The ANCOVA model using treatment and baseline value as covariates will be used for the analysis of last non-missing observation prior to or at Visit 801 and the analysis of maximum percent binding during the analysis period of Visit 2 to Visit 801. Plot of anti-insulin lispro antibody percent binding will be generated based on the MMRM and the ANCOVA models.

A listing of anti-insulin lispro antibody at each visit will be provided. The listing will include anti-insulin lispro antibody status (detected/not detected), anti-insulin lispro antibody percent binding, TEADA status (positive/negative), insulin cross-reactivity status, insulin cross-reactivity percent binding for the safety population.

Subgroup analysis for the following selected efficacy and safety variables will be performed by the TEADA status during the treatment period of Visit2 to Visit 801:

- Use data prior to discontinuation of IP:
    - HbA1c and change from baseline in HbA1c
    - 1-hour and 2-hour PPG excursions
    - basal, prandial, and total insulin dose
    - event rate (per patient per year) of overall hypoglycemic events
- Use all data regardless of IP use:
    - treatment-emergent injection site reaction and hypersensitivity reaction

The analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model for the primary analysis and the HbA1c data prior to discontinuation of IP. The model will include additional fixed terms of subgroup, subgroup by treatment interaction, subgroup by visit interaction, and 3-way interaction of treatment, subgroup, and visit.

The PPG excursions will be analyzed by the ANCOVA model same as the model specified in Section 6.11.2. with data collected before permanent discontinuation of IP. The model will include additional terms of subgroup, subgroup by treatment interaction, subgroup by visit interaction, and 3-way interaction of treatment, subgroup, and visit.

The subgroup analysis for insulin dose will use the MMRM model specified in Section 6.11.5 using data collected before permanent discontinuation of IP. The model will include additional fixed terms of subgroup, subgroup by treatment interaction, subgroup by visit interaction, and 3-way interaction of treatment, subgroup and visit.

The treatment emergent injection site reaction and hypersensitivity reaction will be analyzed by a logistic regression model including terms of treatment, subgroup, and treatment by subgroup interaction. All data regardless of IP use will be used for this analysis.

The negative binomial regression model specified in Table 6.5 with additional terms of subgroup, treatment by subgroup interaction will be used for the subgroup analysis of overall hypoglycemia event rate while on IP.

The interaction effects (3-way for MMRM and 2-way for ANCOVA/logistic regression model/negative binomial regression model) will be evaluated using a significance level of 0.10, unadjusted. If the interaction effect is significant ($p<0.10$), separate analyses without the terms related to the subgroup will be performed for each subpopulation.

6.12.8. Patient Narratives

Patient narratives will be provided for all patients in the study who experience any of the following "notable" events prior to data cutoff for the submission:

- deaths
- serious adverse events
- discontinuations from study (or study drug) due to AEs
- pregnancy

A list of patients who meet the criteria for narratives will be provided.

6.13. Subgroup Analyses

6.13.1. Subgroup Analyses for HbA1c

The following subgroups will be analyzed for HbA1c if there are sufficient numbers of patients per group (for example, at least 10% in each group) using data collected from all randomized patients prior to discontinuation of IP through Week 26:

- age (<40, ≥40 years)
- hemoglobin A1c stratum (≤8.5% vs. >8.5%)
- sex (male vs. female)
- body mass index (<25 vs. ≥25, and <30 vs. ≥30 kg/m^2)
- duration of diabetes (using the median as the cut-off)
- race
- country
- baseline 1-hour PPG excursion (≤ baseline median, > baseline median)
- baseline 1-hour PPG (PPG ≤180 mg/dl, >180 mg/dl)

- baseline 2-hour PPG excursion (≤ baseline median, > baseline median)
- baseline 2-hour PPG (PPG ≤180 mg/dl, >180 mg/dl)
- type of basal insulin during the lead-in period (glargine U-100 vs. degludec U-100)
- prandial insulin dosing plan (carbohydrate counting or pattern adjustment)

Analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model that includes 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 subgroup. The interaction of subgroup and treatment at the primary endpoint will be evaluated to assess the treatment by subgroup interaction. When analyzing HbA1c stratum as a subgroup the baseline HbA1c will not be included as a covariate to avoid confounding. The subgroup interaction effect will be evaluated using a significance level of 0.10, unadjusted.

Additional subgroup analyses may also be performed.

6.13.2. Subgroup Analyses for Hypoglycemic Events

For the documented symptomatic hypoglycemia based on the thresholds of blood glucose ≤70 mg/dL, the following subgroups will be analyzed using data collected from all randomized patients prior to discontinuation of IP through Week 26:

- age (<40, ≥40 years)
- hemoglobin A1c stratum (≤8.5% vs. >8.5%)
- region
- type of basal insulin during the lead-in period (glargine U-100 vs. degludec U-100)
- prandial insulin dosing plan (carbohydrate counting or pattern adjustment)

The event rate and incidence will be analyzed using the same model specified in Table 6.5 with the addition of factors for subgroup, and 2-way interaction of subgroup and treatment. The 2-way interaction will be used to evaluate treatment by subgroup interaction.

6.14. Interim Analyses and Data Monitoring

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

6.15. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Non-Serious Adverse Events are summarized by treatment group and MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may be excluded if a 5% threshold is chosen. Allowable thresholds include 0% (all events), 1%, 2%, 3%, 4%, and 5%.
- Adverse event reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. Novel Coronavirus (COVID-19) Impact

This section lists some of the potential statistical analyses may be performed at the final database lock due to the impact of COVID-19 pandemic, if data guarantee.

7.1 Patients' Study Visits Impacted by COVID-19

Percentage and count of randomized participants with study visits impacted by COVID-19 will be compared by treatment groups. These participants includes, but not limited to six kinds, patients with any visit not performed, patients with any on-site visit changed to remote, patients with HbA1C missing, patients with 1,5 AG result missing, patients with MMTT result missing and patients with direct to patient drug supply. Listing of patients with study visits impacted by COVID-19 will also be provided.

For each of the six situations, a separate summary table and listing will be provided.

7.2 Protocol Deviation

Percentage and count of randomized participants having protocol deviation related to COVID-19 pandemic will be summarized by treatment. No statistical comparison between treatment groups will be conducted.

A listing of all randomized participants having protocol deviation due to COVID-19 pandemic will be provided.

A summary table and listing of all randomized participants having significant protocol deviation due to COVID-19 pandemic will also be provided.

7.3 Patient Disposition

A summary table for dispositon reasons of all enrolled participants who discontinue study during the lead-in period due to COVID-19 may be provided. For the treatment period, a summary table for dispositon reasons of all randomized participants who discontinue study or study treatment due to COVID-19 may be provided. For the safety follow-up period, a summary table for dispositon reasons of all randomized participants in the safety follow-up period who discontinue study due to COVID-19 may be provided.

7.4 COVID-19 Infection

Percentage and count of randomized participants having COVID-19 infection, including death due to COVID-19 pandemic from lead-in period to safety follow-up period will be summarized by treatment.

A listing of randomized participants who had COVID-19 infection, including death due to COVID-19 infection, from lead-in period to safety follow-up period will be provided.

7.5 Some Mitigation Procedures

Some mitigation procedures are conducted to reduce the impact of COVID-19 during the study, which include direct to patient drug supply, IP (bolus insulin) local purchase and Visit 7 and Visit 8 combined.

Summary and listing of IP local purchase due to the COVID-19 pandemic will be provided. Randomized participants with Visit 7 and Visit 8 combined due to the COVID-19 pandemic will be summarized by treatment.

7.6 Sensitivity Analysis for Efficacy

The impact of COVID-19 on the efficacy of IP on the patients may come from different aspects such as prolonged treatment interruptions due to COVID-19 illness or control measures, study or treatment discontinuations due to COVID-19 illness or control measures, death due to COVID-19 and the usage of protocol prohibited medications to treat COVID-19. CCI [redacted]

A sensentivity analysis will be conducted on the randomized patients without essential impact of COVID-19, i.e., the randomized patients who can't be classified into the above two groups. The MMRM and ANCOVA models as described in Section 6.11.1 and Section 6.11.3 respectively will be repeated as the models for the sensitivity analysis. If the conclusion differs from that of all randomized patients, the data and analysis will be further investigated.

8. Unblinding Plan

The blinding and unblinding plan will be provided in a separate document stored in the Trial Master File.

9. References

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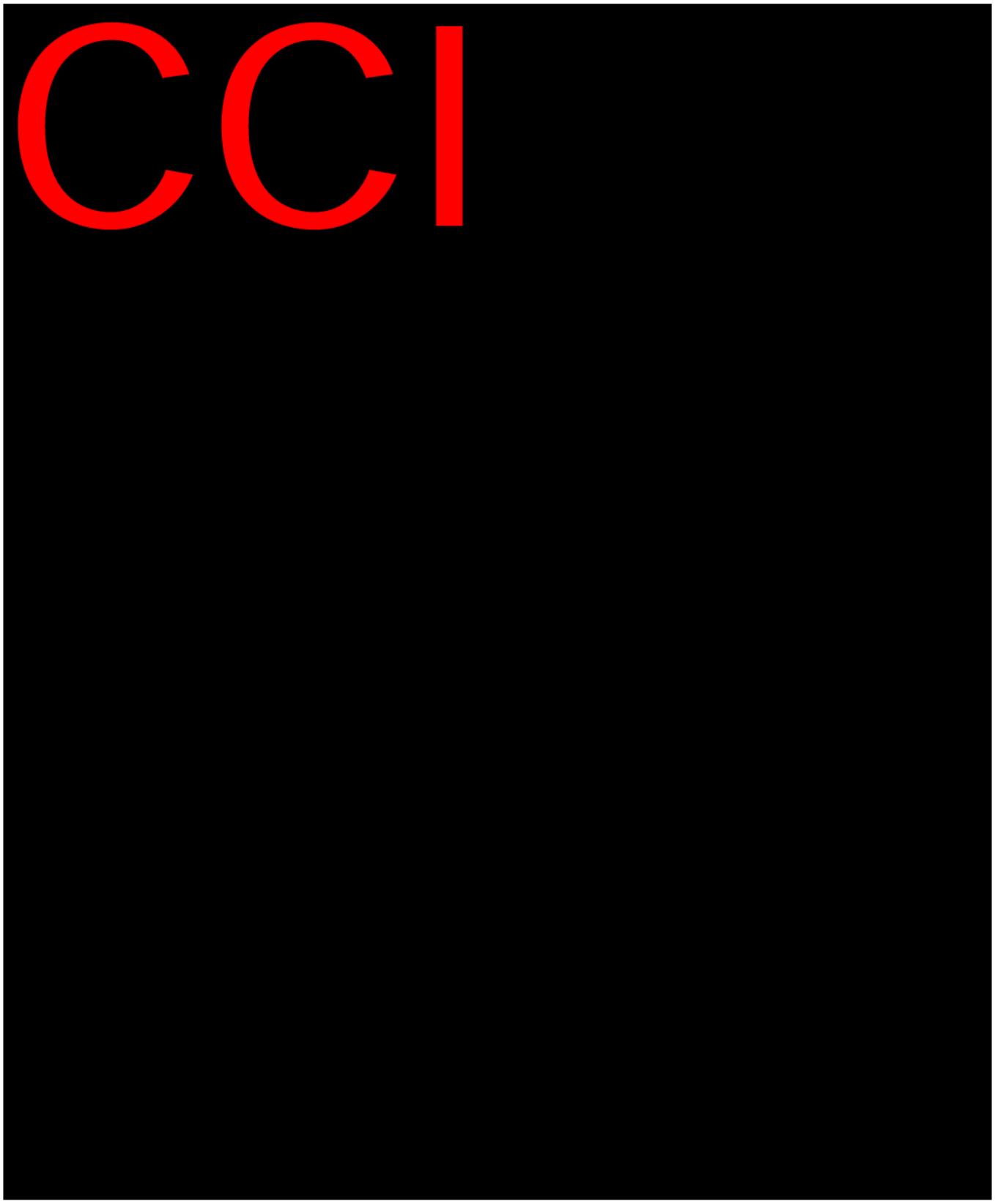
10. Appendices

Appendix 1. Empirical Estimation of Relative Event Rate

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Approver: PPD

Approval Date & Time: 18-Jan-2022 03:01:50 GMT

Signature meaning: Approved