U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | BLA 761109 |
| **Supplement #:** | 004 |
| **Drug Name:** | Lyumjev (insulin lispro) |
| **Indication(s):** | To improve glycemic control in pediatric patients with diabetes mellitus |
| **Applicant:** | Eli Lilly |
| **Date(s):** | Receipt date: 12/14/2021 |
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| **Review Priority:** | Standard |
| **Biometrics Division:** | DB II |
| **Statistical Reviewer:** | Wenda Tu |
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| **Medical Division:** | DDLO |
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**Keywords:**

Non-inferiority design, Pediatric study, Analysis of covariance, return-to-baseline imputation, tipping point analysis, shrinkage analysis, Bayesian Hierarchical Modelling, insulin product

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# 1 EXECUTIVE SUMMARY

The applicant, Eli Lilly and Company, submitted this supplemental Biologics License Application (sBLA) for LY900014 (Lyumjev®) in support of its product label update regarding pediatric indication. LY900014 is a rapid-acting formulation of insulin lispro. In 2020, It was approved for both subcutaneous (including delivery via multiple daily injection (MDI) and continuous insulin infusion (CSII)) and intravenous administration for improvement of glycemic control among adults with diabetes. In the current submission, the Applicant proposed to expand the indication to include pediatric patients with diabetes, and to add administration via CSII as a condition of use in the pediatric population.

Data from two clinical studies were included in this submission to support the pediatric indication: the Phase III Study I8B-MC-ITSB (ITSB) and the Phase I Study I8B-MC-ITSA (ITSA). This statistical review focuses on the Phase III Study ITSB. In fulfillment of PREA PMR 3874-1, this study was conducted to evaluate the safety and efficacy of LY900014 in type 1 diabetes (T1D) patients 1 to <18 years of age, with treatment delivered via MDI.

## 1.1 Brief overview of Clinical Study

Study ITSB was a multi-center, randomized, parallel-group, active-controlled study intended to evaluate mealtime and postmeal LY900014 compared to mealtime Humalog®[1] among T1D subjects 1 to < 18 years of age. The study consisted of a one-week screening period, a four-week lead-in period, a 26-week treatment period and a two-week follow-up period. A total of 716 subjects were randomized in a 2:2:1 ratio to the three arms: Mealtime LY900014 (LY900014), Mealtime Humalog (Humalog) and Postmeal LY900014 (LY900014+20[2]). The primary objective of the study was to demonstrate that LY900014 was non-inferior (non-inferiority [NI] margin=0.4) to Humalog with respect to glycemic control, as evaluated by the primary endpoint of change from baseline in HbA1c at Week 26.

## 1.2 Major Statistical Issues

No major statistical issues have been identified in this review. The study has relatively low missing data (6.0% of the participants had missing primary endpoint measures). Missing endpoints were multiply imputed based on the return-to-baseline method. For primary efficacy analyses, the applicant applied an ANCOVA adjusted for treatment, baseline HbA1c and stratification factors used in the study.

As a minor issue, a statistically significant *treatment-by-race* interaction effect was detected (p-value =0.048). In the Applicant's analysis on race, there were six racial categories, with *white* making up 90% of the full population. The reviewer re-conducted the race subgroup analysis

[1] Humalog® is insulin lispro injection product currently on the market.
[2] For the postmeal LY900014 arm, LY900014 was administered up to 20 minutes after the start of a meal. The arm is hence denoted as LY900014 +20.

based on *white vs. non-white* and found no significant differences between these two groups. Additionally, the treatment-by-race effect is not statistically significant based on the grouping of *white vs non-white* (p-value = 0.25).

Another minor issue is with respect to the technicality of missing data imputation. In brief, the return-to-baseline procedure implemented by the Applicant is slightly different from what the Agency proposed (Section 3.2.2). The statistical reviewer performed missing data imputation based on that method proposed by the Agency, which produced identical numerical results (up to two decimal places) regarding the estimated treatment effect of HbA1c (%) change from baseline.

## 1.3 Collective Evidence

Results from the primary efficacy analyses demonstrated that both Mealtime LY900014 and post-mealtime LY900014 are non-inferior to Humalog in terms of glycemic control. Key efficacy results are summarized in Table 1. Additionally, results from sensitivity analyses demonstrated robustness of the primary efficacy results to the untestable assumptions on missing data (Table 11 & Figure 2). Subgroup analyses on the primary efficacy endpoint suggested that non-inferiority of LY900014 to Humalog was not impacted by age (1 to < 12 years vs 12 years to < 18 years), gender (male vs female), race (white vs non-white) or region (East Asia, Europe, North America, Other Region 1 and Other Region 2) (Table 9). In addition, no elevated risk of Level 2 or Level 3 hypoglycemic events was found among the subjects treated with LY900014 compared to subjects treated with Humalog (Table 7 & Table 8).

**Table 1: Summary of Efficacy Results, Study I8B-MC-ITSB**

| Treatment (# of Randomized Subjects) | HbA1c (%), Lsmean (SE) | | Lsmean Difference (vs Humalog) at Week 26 (95% CI) |
|---|---|---|---|
| | Baseline | Change from Baseline at Week 26 | |
| Humalog (N = 298) | 7.81 (0.05) | 0.06 (0.05) | |
| LY900014 (N = 280) | 7.78 (0.05) | 0.06 (0.05) | -0.01 (-0.15, 0.14) |
| LY900014 +20 (N = 138) | 7.77 (0.07) | 0.06 (0.08) | -0.00 (-0.18, 0.18) |

## 1.4 Conclusion and Recommendations

Statistical analyses based on the clinical data from the Phase III Study I8B-MC-ITSB have demonstrated robust evidence to support the effectiveness of LY900014 (both mealtime and postmeal, administered via MDI) regarding glycemic control among pediatric patients (1 to < 18 years) with T1D. However, as the proposed pediatric indication includes both T1D and T2D, with administration via CSII as a condition of use, inputs from other review disciplines are needed for the final approval of the proposed label update.

# 2 INTRODUCTION

## 2.1 Overview

LY900014 (Lyumjev®) , a rapid-acting formulation of insulin lispro, was approved by the FDA in 2020 for glycemic control among adults with diabetes. The drug is available under two dose concentrations: 100 U/mL and 200 U/mL. The approved routes of administration include both subcutaneous (including delivery via MDI and CSII) and intravenous administration. In this sBLA, the applicant plans to expand the indication to pediatric patients (aged 1 to 17 years) with diabetes. Data and analysis results from two clinical studies are used to support the pediatric indication: the Phase III Study I8B-MC-ITSB and the Phase I Study I8B-MC-ITSA. Both studies were conducted on pediatric patients with T1D, with the drug administered via MDI. Additional PK/PD modelling and simulation were performed to support the use among patients with T2D and the route of administration via CSII.

The Phase III Study ITSB started on April 7, 2019, and completed on July 2, 2021. The study database was locked on July 16, 2021. An overview of the study is presented in Table 2.

**Table 2: Overview of Study I8B-MC-ITSB**

| Trial ID | Design* | Treatment** (Sample Size) | Objectives | Endpoints/Analyses |
|---|---|---|---|---|
| I8B-MC-ITSB (ITSB)<br><br>Phase III | MC, R, PG, AC trial (1-week screening + 4-week lead-in + 26 week treatment + 2-week follow up) | **Mealtime LY90014 (LY900014)** (N= 298 )<br><br>**Mealtime Humalog (Humalog)** (N = 280 )<br><br>**Post Mealtime LY900014 (LY900014+20)** (N = 138 ) | **Primary objective**: LY900014 is noninferior to Humalog with respect to glycemic control.<br><br>**Key secondary objectives**:<br>1. LY900014+20 is noninferior to Humalog with respect to glycemic control<br>2. LY900014 is superior to Humalog with respect to glycemic control. | **Primary endpoint:** Change from baseline in HbA1c at Week 26.<br><br>**Secondary endpoints[3]:** Incidence of HbA1c < 7.0% and < 7.5%<br>Daily basal and prandial insulin dose<br>Self-monitored blood glucose (SMBG) profiles<br><br>**Primary Analysis:** Each analysis was conducted on all randomized participants regardless of the study drug use. An ANCOVA[4] with missing data multiply imputed based on the return-to-baseline method was performed. NI (or superiority) would be declared if the upper limit of the 2-sided 95% CI for the LS mean difference (LY900014 – Humalog) was below the NI margin 0.4% (or 0%). |

* MC: multi-center, R: randomized, PG: parallel group, AC: active controlled

[3] The study did not have any key secondary endpoints. This is consistent with the adult studies where HbA1c change from baseline was the only efficacy endpoint intended for labelling.
[4] The ANCOVA model: A1c change from baseline ~ treatment + baseline A1c + pooled country + type of basal insulin (insulin glargine, detemir, or degludec) + age group (1 to < 12 years vs. 12 to < 18 years)

** For all treatment arms, the dose strength was 100 U/mL. Subjects from the LY900014 arm and the Humalog arm received treatment immediately (0 to 2 mins) prior to each meal in a double-blind manner. Subjects from the LY900014+20 arm received open-label LY900014 up to 20 mins after start of a meal.

### 2.2 Data Sources

The Electronic Document Room (EDR) locations for this submission is \\CDSESUB1\evsprod\BLA761109\0372. Datasets for Study ITSB (both in ADAM format and SDTM format) and the programming codes for both the primary and the key secondary efficacy analyses can be found under the subdirectory: m5\datasets\i8b-mc-itsb.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

No issues have been identified with respect to data and analysis quality.

### 3.2 Evaluation of Efficacy

#### 3.2.1 Study Design and Endpoints

Study ITSB was a multi-center, randomized, parallel-group and active-controlled study designed to assess the efficacy and safety of LY900014 (both mealtime and post-mealtime) in comparison to Humalog among pediatric patients aged 1 to 17 years with T1D. As demonstrated in Figure 2, the study included a one-week screening period, a four-week lead-in period, followed by a 26-week treatment period and a two-week safety follow-up period. During the treatment period, subjects were randomized to one of the three arms: the double-blind arm LY900014, the double-blind arm Humalog, or the open-label arm LY900014 +20 in a 2:2:1 ratio. The study was stratified by the following factors:

- Country,
- HbA1c stratum (≤ 8.0% vs > 8 %) at screening,
- Type of basal insulin at randomization (insulin glargine, detemir, or degludec), and
- Age group (1 to < 12 years vs 12 to < 18 years).

The primary objective of this study was to demonstrate NI of Mealtime LY900014 to Humalog with respect to glycemic control. Key secondary objectives include NI of post mealtime LY900014 to Humalog on glycemic control and superiority of LY900014 (both mealtime and post-prandial) to Humalog on glycemic control. The primary endpoint of the study was HbA1c (%) change from baseline at Week 26. The study did not include any key secondary endpoint.

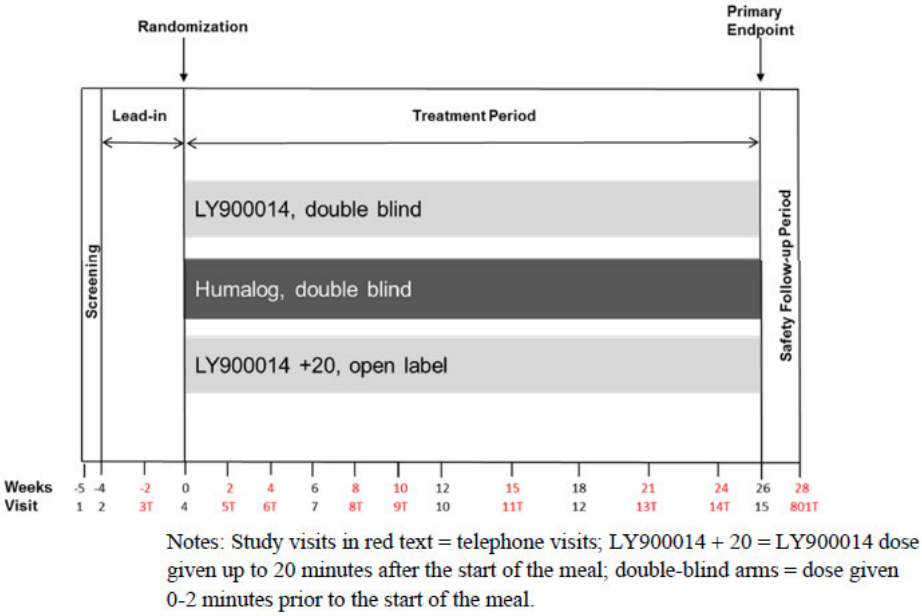


**Figure 1: Design Diagram for Study ITSB**

*Source: Figure ITSB.3.1, CSR*

Sample Size

The sample size for the LY900014 arm and the Humalog arm was determined as follows. Assuming an NI margin of 0.4%, no true difference between the two treatment groups and a standard deviation (SD) of 1.1%, 240 completers for each treatment group provide > 95% power to show NI of LY900014 to Humalog, using the upper limit of a two-sided 95% CI (LY90014 – Humalog). Note that 0.4% was the NI margin used in the adult pivotal studies for LY900014.

With 240 completers required for the Humalog arm, sample size for the LY900014 + 20 arm was determined as follows. Assuming an NI margin of 0.4%, a treatment difference of < 0.07%, 240 completers from Humalog arm and 120 completers from the LY900014 postmeal arm provide approximately 76% power to show NI of LY900014 postmeal to Humalog.

Finally, assuming an overall dropout rate of 15% during 26 weeks of treatment, approximately 708 subjects (N = 283 for the LY900014 arm, N = 283 for the Humalog arm, and N = 142 for the LY900014 postmeal arm) were planned for the study.

In reality, a total of 716 participants, including 280 subjects on LY900014, 298 subjects on Humalog, and 138 subjects on LY900014 +20, were randomized. The dropout rate was lower than the expected 15% (See Section 3 for details). The study appears to have adequate power to achieve the pre-specified objectives.

Primary Endpoint

- Change from baseline in HbA1c (%) at Week 26

Secondary Endpoints (Not Intended for Labelling)

- Incidence of HbA1c < 7.0% and < 7.5%
- Daily basal and prandial insulin dose
- Self-monitored blood glucose (SMBG) profiles

### 3.2.2 Statistical Methodologies

Two estimands were proposed in the study protocol: the intention-to-treat (ITT) estimand and the efficacy estimand. The ITT estimand, which included all data for efficacy analyses regardless of intercurrent events, was used for regulatory purpose, and hence is the focus of this review. Details of the statistical methods under the ITT estimand are described in this section.

Population & Analysis Set
The target population was the ITT population, defined as all randomized subjects, regardless of post-baseline result availability.

Handling of Missing Data
The return-to-baseline approach was employed. Specifically, the patient-level baseline value plus a noise was used to impute missing endpoints. The noise follows a normal distribution with variability estimated from the "washout HbA1c data". The "washout HbA1c data" were derived by subtracting the mean treatment effect (calculated within each treatment arm) from individual non-missing HbA1c values at Week 26. Note that the Applicant's return-to-baseline method slightly differs from the Division recommended method where variability of the imputed endpoints is usually estimated from the primary ANOCOVA model based on completers' data. The reviewer performed the primary analysis based on the Division's preferred method. The reviewer's result and the Applicant's result are identical up to two decimal places.

Primary & Key Secondary Efficacy Analyses
The analysis was performed based on an ANCOVA, with HbA1c change from baseline at Week 26 as the response variable, and treatment, baseline HbA1c, and strata (pooled country, type of basal insulin, and age group) as covariates. The ANCOVA was performed on 1000 imputed datasets and Rubin's Rule was used to combine the analysis results.

Multiplicity Adjustment
A hierarchical testing procedure was used for multiplicity control of the hypothesis testing for the primary and key secondary objectives. Each test was conducted at a two-sided 0.05 level, with the hierarchy specified as below.

- NI test of LY900014 to Humalog (NI margin=0.4)
- NI test of LY900014 + 20 to Humalog (NI margin=0.4)
- Superiority test of LY900014 to Humalog

Sensitivity Analysis
A one-way tipping point analysis was performed for sensitivity analysis. Specifically, a penalty (delta) was added to the imputed values of the experimental arm and the same ANCOVA as applied to the primary analysis was performed on the delta-adjusted dataset to see whether the conclusion of the primary analysis was overturned. If not, the delta penalty was incremented, and

the process was repeated until the primary result was overturned. The primary result would be robust to missing data, if the delta required to overturn the primary result was not a plausible scenario in a real-word setting. Imputation under the NI null method was included as a special case of this tipping point analysis.

Additionally, the reviewer performed a two-way tipping point analysis by tipping both the experimental arm and the control arm, following a similar procedure as described above.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A summary of patient disposition for Study ITSB is presented in Table 3. All randomized subjects received at least one dose of the study drug. No notable difference is observed across the treatment arms in terms of study disposition or treatment disposition. The study discontinuation rates are 3.4% (Humalog) , 5.0% (LY900014) and 2.2% (LY900014 +20). The treatment discontinuation rates are 3.4% (Humalog) , 5.0% (LY900014) and 1.4% (LY900014 +20). Primary endpoint measurements are missing at 5.4% for Humalog, 7.1% for LY900014, and 5.1% for LY900014 +20. No retrieved dropout data are available in this study[5].

**Table 3: Patient Disposition, All Randomized Patients**

| **Treatment Arms (# of Randomized Subjects)** | **Humalog (N = 298)** | **LY900014 (N = 280)** | **LY900014 +20 (N = 138)** | **Total (N = 716)** |
|---|---|---|---|---|
| **Study Disposition** | | | | |
| Completed | 288 (96.6) | 266 (95.0) | 135 (97.8) | 689 (96.2) |
| Discontinued | 10 (3.4) | 14 (5.0) | 3 (2.2) | 27 (3.8) |
| **Reasons for Study Discontinuation** | | | | |
| Adverse Event | 0 | 2 (0.7) | 0 | 2 (0.3) |
| Other | 2 (0.7) | 6 (2.1) | 1 (0.7) | 9 (1.3) |
| Protocol Deviation | 1 (0.3) | 0 | 0 | 1 (0.1) |
| Withdrawal By Subject | 7 (2.3) | 6 (2.1) | 2 (1.4) | 15 (2.1) |
| **Treatment Disposition** | | | | |
| Completed | 288 (96.6) | 266 (95.0) | 136 (98.6) | 690 (96.4) |
| Discontinued | 10 (3.4) | 14 (5.0) | 2 (1.4) | 26 (3.6) |
| **Reasons for Treatment Discontinuation** | | | | |
| Adverse Event | 0 | 2 (0.7) | 0 | 2 (0.3) |
| Lack of Efficacy | 1 (0.3) | 1 (0.4) | 0 | 2 (0.3) |
| Non-Compliance with Study Drug | 1 (0.3) | 1 (0.4) | 0 | 2 (0.3) |
| Other | 2 (0.7) | 3 (1.1) | 0 | 5 (0.7) |
| Physical Decision | 0 | 1 (0.4) | 0 | 1 (0.1) |
| Protocol Deviation | 1 (0.3) | 0 | 0 | 1 (0.1) |
| Withdrawal By Subject | 5 (1.7) | 6 (2.1) | 2 (1.4) | 13 (1.8) |
| **Missed primary endpoints*** | 16 (5.4) | 20 (7.1) | 7 (5.1) | 43 (6.0) |

* Information on "Missed Primary Endpoints" was provided by the reviewer based on the datasets: adsl and ada1c.

*Source: Table ITSB.8.4 , CSR & reviewer's analysis.*

A summary of patient demographics and baseline characteristics is presented in Table 4. Based on the summary, demographics and baseline characteristics are well-balanced across the three

[5] The Applicant did not provide any reason as to why retrieved dropout data is not available.

study arms. Specifically, the percentages of subjects on the three lead-in basal insulins are comparable across the three arms.

**Table 4: Patient Demographics and Baseline Characteristics, All Randomized Patients**

| Treatment Arms (# of Randomized Patients) | Humalog (N = 298) | LY900014 (N = 280) | LY900014 + 20 (N = 138) | Total (N = 716) |
|---|---|---|---|---|
| **Age** | | | | |
| Mean (SD) | 12.39 (3.18) | 12.10 (3.42) | 12.32 (3.75) | 12.26 (3.39) |
| Minimum, Maximum | 3, 17 | 3, 17 | 4, 17 | 3, 17 |
| 1 to < 12 years, n (%) | 105 (35.2) | 98 (35.0) | 50 (36.2) | 253 (35.3) |
| 12 to < 18 years, n (%) | 193 (64.8) | 182 (65.0) | 88 (63.8) | 463 (64.7) |
| **Sex, n (%)** | | | | |
| Female | 140 (47.0) | 144 (51.4) | 65 (47.1) | 349 (48.7) |
| Male | 158 (53.0) | 136 (48.6) | 73 (52.9) | 367 (51.3) |
| **Ethnicity, n (%)*** | | | | |
| Hispanic or Latino | 12 (24.0) | 12 (22.6) | 6 (25.0) | 30 (23.6) |
| No Hispanic or Latino | 38 (76.0) | 41 (77.4) | 18 (75.0) | 97 (76.4) |
| **Race, n (%)** | | | | |
| American Indian or Alaska Native | 6 (2.0) | 6 (2.1) | 0 | 12 (1.7) |
| Asian | 20 (6.7) | 13 (4.6) | 7 (5.1) | 40 (5.6) |
| Black or African American | 7 (2.3) | 3 (1.1) | 1 (0.7) | 11 (1.5) |
| Multiple | 4 (1.3) | 0 | 1 (0.7) | 5 (0.7) |
| Native Hawaiian/ Other Pacific Islander | 2 (0.7) | 0 | 0 | 2 (0.3) |
| Not Reported | 3 (1.0) | 2 (0.7) | 3 (2.2) | 8 (1.1) |
| White | 256 (85.9) | 256 (91.4) | 126 (91.3) | 638 (89.1) |
| **BMI ($kg/m^2$)** | | | | |
| Mean (SD) | 20.3 (4.19) | 20.5 (4.60) | 20.5 (4.39) | 20.4 (4.39) |
| Minimum, Maximum | 12.8, 38.8 | 11.5, 38.0 | 14.1, 37.3 | 11.5, 38.8 |
| **Duration of Diabetes (years)** | | | | |
| Mean (SD) | 4.7 (3.28) | 4.5 (3.58) | 4.6 (3.32) | 4.6 (3.41) |
| Minimum, Maximum | 0.5, 15.9 | 0.5, 16.5 | 0.5, 15.3 | 0.5, 16.5 |
| **Baseline HbA1c** | | | | |
| Mean (SD) | 7.81 (0.91) | 7.81 (0.87) | 7.77 (0.85) | 7.80 (0.88) |
| ≤ 8.0%, n (%) | 187 (62.8) | 174 (62.1) | 86 (62.3) | 447 (62.4) |
| >8.0%, n (%) | 111 (37.2) | 106 (37.9) | 52 (37.7) | 269 (37.6) |
| **Lead-in Basal Insulin, n (%)** | | | | |
| Insulin degludec | 108 (36.2) | 105 (37.5) | 46 (33.3) | 259 (36.2) |
| Insulin detemir | 26 (8.7) | 23 (8.2) | 16 (11.6) | 65 (9.1) |
| Insulin glargine | 164 (55.0) | 152 (54.3) | 76 (55.1) | 392 (54.7) |

* Only includes responses from US sites.

*Source: Table ITSB.4.2 , CSR*

### 3.2.4 Results and Conclusions

The analysis result for the primary endpoint based on the methods described in Section 3.2.2 is presented in Table 5. The Lsmean difference (95% CI) in HbA1c change from baseline at Week 26 is -0.01 (-0.15, 0.14) for LY900014 vs. Humalog, and -0.00 (-0.18, 0.18) for LY900014 +20 vs. Humalog. Based on this analysis result, both LY900014 and LY900014 +20 were found non-inferior to Humalog. However, the analysis fails to demonstrate superiority of LY900014 to Humalog.

**Table 5: Analysis of HbA1c at Baseline and at Week 26, All Randomized Subjects**

| Treatment Arm | HbA1c (%), Lsmean (SE) | | | Lsmean Difference (Mealtime/Postmeal LY900014 vs Humalog) at Week 26 (95% CI) |
|---|---|---|---|---|
| | Baseline | Week 26 | Change from Baseline at Week 26 | |
| Humalog (N = 298) | 7.81 (0.05) | 7.87 (0.05) | 0.06 (0.05) | |
| LY900014 (N = 280) | 7.78 (0.05) | 7.86 (0.05) | 0.06 (0.05) | -0.01 (-0.15, 0.14) |
| LY900014 +20 (N = 138) | 7.77 (0.07) | 7.86 (0.08) | 0.06 (0.08) | -0.00 (-0.18, 0.18) |

*Source: Table ITSB.5.2, P58, CSR (results verified by the reviewer)*

For the sensitivity analysis, the applicant conducted the one-way tipping point analysis to investigate the impact of missing data on the primary analysis results. The one-way tipping point analysis, which imposed an incremental penalty on the imputed endpoints in the LY900014 arm, shows that the primary analysis result (NI of LY900014 to Humalog) hold until the penalty reaches a value of 3.4%, which is an unlikely situation in the real-world setting. More details of the one-way tipping point analysis can be found in Table 11 in the Appendix.

Since the return-to-baseline imputation uses the same imputation model for each treatment arm, this method can attenuate treatment differences and make it easier to conclude non-inferiority when it does not exist. Based on the *FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness*, imputation of missing data under the inferiority null hypothesis was performed; *i.e.*, the NI margin (0.4) was added to the imputed endpoints from the LY900014 arm. The analysis result, displayed in Table 11 as part of the one-way tipping point analysis result, shows a point estimate of 0.02 with its 95% confidence interval (-0.13, 0.17), suggesting that NI still holds.

The two-way tipping point analysis conducted by the reviewer further corroborated the robustness of the primary analysis. A heatmap was generated based on the two-way tipping point analysis results. As presented in **Error! Reference source not found.**, the primary result was overturned only when an implausible penalty (or benefit) was added to the treatment arm (or the control arm).

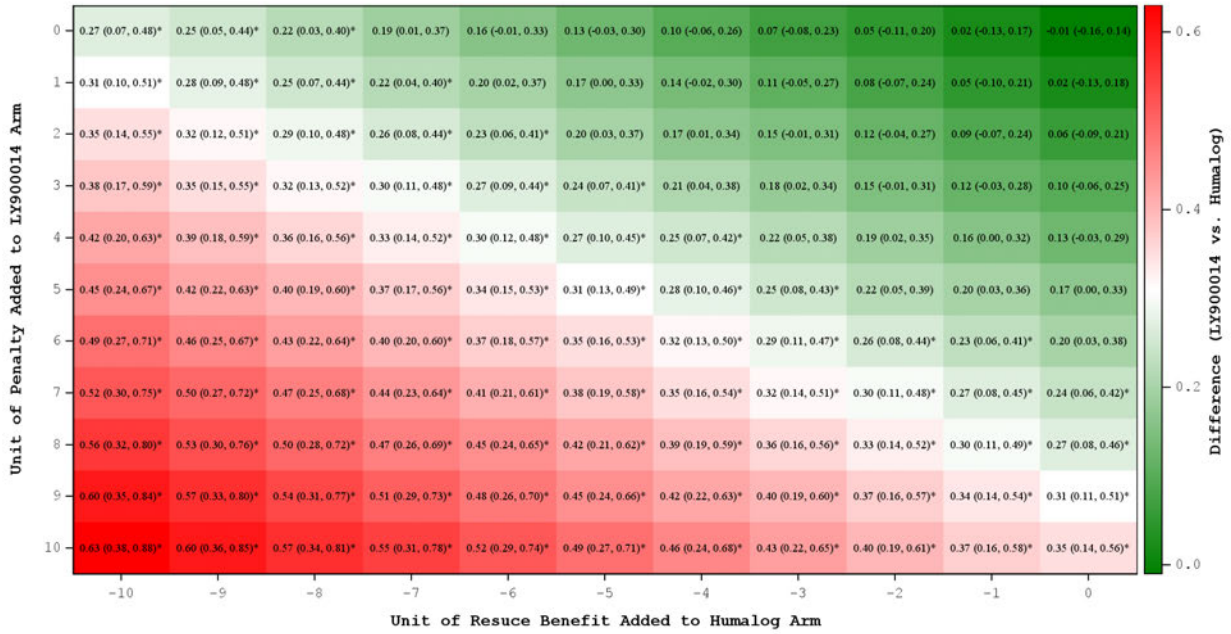


**Figure 2: Heatmap for Two-Way Tipping Point Analysis for Primary Efficacy Analysis**

*Note: Each unit on marked on the x-axis and y-axis equals 0.5. The value in each cell is the mean difference (95% CI) in HbA1c (%) change from baseline between LY900014 and Humalog. Asterisks indicate that the primary result is tipped.*

Because there were no pre-specified key secondary endpoints, analysis results for the secondary endpoints: incidence of HbA1c < 7.0% and HbA1c < 7.5% are presented below in Table 6, descriptively. The analysis was conducted based on a longitudinal logistic regression, with treatment, time, baseline HbA1c, baseline HbA1c-by-time, and treatment-by-time as covariates and an unstructured variance-covariance structure. The analysis set included data collected from subjects with at least one non-missing post-baseline value of the response variable, up to Week 26 prior to treatment discontinuation. According to the analysis results, no statistical difference was found between the treatment arms and the control arm with respect to the proportion of subjects achieving the two HbA1c targets. This analysis provides consistent results to the primary analysis findings.

**Table 6: Proportion of Subjects Achieving HbA1c Targets at Week 26**

| | HbA1c < 7% | | HbA1c < 7.5% | |
|---|---|---|---|---|
| Treatment (Number of Randomized Subjects) | Number (%) of Subjects Achieving the Target | Odds Ratio (Treatment/Control) (95% CI) | Number (%) of Subjects Achieving the Target | Odds Ratio (Treatment/Control) (95% CI) |
| Humalog (N = 298) | 56 (20.00) | | 112 (40.00) | |
| LY900014 (N = 280) | 57 (21.92) | 1.23 (0.76, 2.00) | 97 (37.31) | 0.84 (0.55, 1.27) |
| LY900014 +20 (N = 138) | 25 (19.08) | 0.93 (0.49, 1.75) | 43 (32.82) | 0.62 (0.36, 1.08) |

*Source: Table ITSB.5.3, CSR*

## 3.3 Evaluation of Safety

Both Level 2 and Level 3[6] hypoglycemia events were investigated in this study among the safety population, defined as all randomized subjects who received at least one dose of the treatment. The analysis period was from Week 0 to Week 26 (the end of the treatment period). Since insulin lispro is fast acting insulin with short half-life, severe hypoglycemia after treatment discontinuation is not expected. The safety analyses did not include the two-week safety follow-up where subjects discontinued the assigned treatment and switched back to their previous insulin regimens.

For both Level 2 and Level 3 hypoglycemia, event incidence was analyzed using a logistic regression adjusted for treatment and age groups. The event rate of Level 2 hypoglycemia was analyzed with a negative binomial regression adjusted for treatment and age groups, and offset by exposure time (Table 7). Due to limited occurrences, episodes of severe hypoglycemia were summarized descriptively only (Table 8). No significant differences were detected across the three treatment arms.

**Table 7: Summary of Hypoglycemia < 54 mg/dL, Week 0 to Week 26, Safety Population**

| | Incidence | | Event Rate* per patient-year | |
|---|---|---|---|---|
| Treatment | # of subjects with hypoglycemia (%) | Odds ratio (95% CI) | Mean (SD) | Relative Rate (95% CI) |
| Humalog (N = 298) | 241 (80.9) | | 16.7 (21.5) | |
| LY900014 (N = 280) | 228 (81.4) | vs. Humalog 1.04 (0.68, 1.57) | 16.0 (19.9) | vs. Humalog 0.96 (0.78, 1.19) |
| LY900014 +20 (N = 138) | 103 (74.6) | vs. Humalog 0.69 (0.43, 1.12) vs. LY900014 0.67 (0.41, 1.09) | 17.8 (23.6) | vs. Humalog 1.07 (0.82, 1.39) vs. LY900014 1.10 (0.85, 1.44) |

*Source: Table ITSB.8.72, CSR*

**Table 8: Summary of Severe Hypoglycemia, Week 0 to Week 26, Safety Population**

| | Incidence | | Event |
|---|---|---|---|
| Treatment | # of subjects with hypoglycemia (%) | Odds ratio (95% CI) | # of episodes |
| Humalog (N = 298) | 3 (1.01) | | 3 |
| LY900014 (N = 280) | 3 (1.07) | vs. Humalog 1.07 (0.25, 4.56) | 3 |
| LY900014 +20 (N = 138) | 0 | vs. Humalog 0.30 (0.02, 5.41) vs. LY900014 0.28 (0.02, 5.06) | 0 |

[6] Per American Diabetes Association definition, Level 2 hypoglycemia is featured by glucose level <54 mg/dl (3.0 mmol/L), and Level 3 hypoglycemia refers to hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery.

*Source: Table ITSB.8.72, CSR*

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses on HbA1c (%) change from baseline were conducted with respect to the patient's baseline characteristics: sex (Male or Female), region (East Asia, Europe, North America, Other Region 1, and Other Region 2[7]), race (White and non-white), and age (1 to < 12 years, and 12 to < 18 years). Each analysis applied the same statistical method as the corresponding primary efficacy analysis (*i.e.,* ANCOVA models with missing primary endpoints imputed based return-to-baseline). For each baseline characteristic, interactions between subgroups and treatment arms were tested.

Additionally, the Bayesian shrinkage analyses based on the sample estimates were performed. For a given baseline characteristic (e.g., sex), when estimating the treatment effect within a subgroup (e.g., the male subgroup), the shrinkage method borrows information from the other subgroup(s) (the female subgroup), and thus is considered a "weighted" average of the sample estimate and the overall estimate. The weights are based on the ratio of the between-subgroup variability to the within-subgroup variability. A small ratio indicates a small between-subgroup variability relative to the within-subgroup variability. Consequently, more weight is put on the overall estimate, and more shrinkage is applied.

For a given baseline characteristic with *k* subgroups, let $Y_i$ ($i$ = 1, ... $k$) be the observed sample estimate of the treatment effect in subgroup *i*. The shrinkage analysis in this review assumes the following:

- $Y_i \sim N(\mu_i, \sigma_i^2)$, where $\mu_i$ is the expected treatment effect for subgroup *i*, and $\sigma_i^2$ is the within-subgroup variance
- $\sigma_i^2$ is set to the variance for the sample estimate
- $\mu_i \sim N(\mu, \tau^2)$, where $\mu \sim N(0, (4)^2)$, and $1/\tau^2 \sim$ Gamma (0.001, 0.001)

The last assumption stated that the expected treatment effect for all *k* subgroups share a common normal distribution centered at $\mu$ and with variance $\tau^2$. A non-informative prior, as specified above, was applied to this normal distribution. A standard deviation of 4 was chosen for the centrality parameter $\mu$, so that its standard deviation was approximately four times the subject-level standard deviation, which was estimated to be around 1 based on the primary analysis results presented in Table 5.

## 4.1 Gender, Race, Age, and Geographic Region

The sample estimates and the shrinkage estimates of the treatment difference with respect to HbA1c change from baseline at Week 26 are presented in Table 9. Findings from the primary efficacy analyses (i.e., non-inferiority [but no superiority] of the investigational drug to the

[7] Other Region 1 consisted of Brazil and Israel; Other Region 2 consisted of Russia and Ukraine.

control) generally hold within the subgroups. Of note, the upper bounds of the 95% confidence intervals (as well as the credible intervals) for *East Asia*, *Other Region 1*, and *non-white* cross the NI margin of 0.4 due to small sample sizes. Additionally, the upper bound of the 95% confidence interval for *Europe* stays below zero. However, the 95% credible interval of *Europe* based on the shrinkage method crosses zero by borrowing information from the other region categories. No statistically significant subgroup-by-treatment effect was detected by the reviewer (Table 9).

**Table 9: Sample and shrinkage Estimates of HbA1c % Change from Baseline within Subgroups, ITT Population**

| | | **LY900014 vs Humalog (N = 280)** | | | **LY900014 +20 vs Humalog (N = 138)** | | |
|---|---|---|---|---|---|---|---|
| **Overall (95% CI)** | | **-0.01 (-0.15, 0.14)** | | | **-0.00 (-0.18, 0.18)** | | |
| | | **Sample (95% CI)** | **Shrinkage (95% CI)** | **n** | **Sample (95% CI)** | **Shrinkage (95% CI)** | **n** |
| Sex | Male | -0.03 (-0.22, 0.17) | -0.02 (-0.19, 0.16) | 136 | 0.01 (-0.22, 0.25) | 0.00 (-0.17, 0.18) | 73 |
| | Female | 0.03 (-0.20, 0.25) | 0.02 (-0.16, 0.19) | 144 | -0.03 (-0.30, 0.25) | -0.02 (-0.25, 0.21) | 65 |
| Region | East Asia | 0.02 (-1.25, 1.29) | 0.00 (-0.47, 0.50) | 10 | -0.23 (-1.69, 1.22) | -0.00 (-0.41, 0.35) | 6 |
| | Europe | -0.31 (-0.58, -0.04) | -0.16 (-0.46, 0.08) | 84 | 0.08 (-0.25, 0.41) | 0.03 (-0.20, 0.27) | 39 |
| | North America | 0.05 (-0.23, 0.32) | 0.02 (-0.20, 0.26) | 77 | -0.13 (-0.47, 0.21) | -0.03 (-0.30, 0.20) | 36 |
| | Other Region 1 | 0.23 (-0.19, 0.65) | 0.08 (-0.22, 0.45) | 35 | -0.13 (-0.65, 0.40) | -0.01 (-0.34, 0.25) | 18 |
| | Other Region 2 | 0.13 (-0.10, 0.37) | 0.06 (-0.16, 0.32) | 74 | 0.13 (-0.17, 0.42) | 0.05 (-0.15, 0.28) | 39 |
| Race* | White | -0.03 (-0.18, 0.11) | -0.02 (-0.21, 0.18) | 256 | 0.00 (-0.17, 0.17) | 0.00 (-0.19, 0.19) | 126 |
| | Non-White | 0.27 (-0.52, 1.06) | 0.10 (-0.38, 0.76) | 22 | 0.03 (-1.09, 1.15) | 0.01 (-0.72, 0.75) | 9 |
| Age | 1 to < 12 years | 0.02 (-0.19, 0.24) | 0.01 (-0.16, 0.18) | 98 | 0.13 (-0.13, 0.40) | 0.07 (-0.17, 0.34) | 50 |
| | 12 to < 18 years | -0.03 (-0.22, 0.17) | -0.02 (-0.19, 0.15) | 182 | -0.10 (-0.34, 0.13) | -0.07 (-0.26, 0.12) | 88 |

*Two subjects from LY900014 and three subjects from LY900014 +20 had unreported race.

*Source: reviewer's analysis.*

The Applicant reported a significant treatment-by-race effect using six racial subgroups for race (p-value = 0.048). According to the Applicant's analysis, race *White* was the predominate group and no other race exceeded 10% of the full study population. Table 10 displays the sample estimates of the treatment effect based on the Applicant's analysis. Limited sample sizes for the non-white categories lead to estimates of poor precision, which could be the reason for the statistically significant treatment-by-race effect. The interaction test based on a regrouping of race as *white vs non-white* turns out statistically insignificant (p-value = 0.25).

**Table 10: Sample Estimates of HbA1c % Change from Baseline, Applicant's Subgroup Analysis on Race**

| Race | LY900014 vs Humalog | n | LY900014 +20 vs Humalog | n |
|---|---|---|---|---|
| American Indian or Alaska Native | 1.48<br>(-0.44, 3.41) | 6 | N.A. | 0 |
| Asian | -0.10<br>(-1.27, 1.06) | 13 | -0.26<br>(-1.66, 1.14) | 7 |
| Black or African American | 0.33<br>(-1.47, 2.14) | 3 | -1.04<br>(-3.90, 1.83) | 1 |
| Multiple | N.A. | 0 | N.A.* | 1 |
| Native Hawaiian/ Other Pacific Islander | N.A. | 0 | N.A. | 0 |
| White | -0.03<br>(-0.18, 0.11) | 256 | 0.00<br>(-0.17, 0.17) | 126 |

* The Humalog arm does not have any *Black or African American* on LY900014 +20.

*Source: Table 8.4.2 , CSR*

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

No major statistical issues were identified in this review. As a minor issue, a statistically significant *treatment-by-race* interaction effect was reported by the Applicant (p-value =0.048). In the Applicant's analysis, race was divided into six categories, many of which have very limited sample sizes. In this review, a subgroup analysis based on *white vs non-white* was performed. No alarming differences was found between these two categories. Additionally, according to this new race grouping, the treatment-by-race effect is not statistically significant either.

## 5.2 Collective Evidence

One Phase III trial was conducted to evaluate the safety and efficacy of LY900014 (mealtime or post-mealtime) in comparison to Humalog. The rate of missing primary endpoint measurements are 5.4%, 7.1% and 5.1% for subjects treated with mealtime LY900014, mealtime Humalog, and post-mealtime LY900014, respectively. Missing primary endpoints were multiply imputed based on the return-to-baseline method as the Agency's preferred method.

Results from the primary efficacy analyses have demonstrated that both mealtime LY900014 and post-mealtime LY900014 are non-inferior to Humalog in terms of glycemic control. Descriptive secondary endpoints showed consistent results to the primary analysis. Additionally, sensitivity analyses have demonstrated robustness of the primary efficacy results to the untestable assumptions on missing data (Table 11and Figure 2). Subgroup analyses on the primary efficacy endpoint suggested that non-inferiority of LY900014 to Humalog was not impacted by age (1 to < 12 years vs 12 years to < 18 years), gender (male vs female), race (white vs non-white) or

region (East Asia, Europe, North America, Other Region 1 and Other Region 2). In addition, safety analysis did not find an elevated risk of Level 2 or Level 3 hypoglycemic events among the Lyumjev-treated subjects compared to the Humalog-treated subjects (Table 7 and Table 8).

## 5.3 Conclusions and Recommendations

Statistical analyses on the clinical data collected from the Phase III study I8B-MC-ITSB have demonstrated non-inferiority of mealtime LY900014 to Humalog and non-inferiority of post-mealtime LY900014 to Humalog, both administered via MDI, in terms of glycemic control in pediatric patients with T1D. These results provide statistical evidence to support the proposed indication for T1D among pediatric patients. However, since the proposed pediatric indication includes both T1D and T2D, with administration via CSII as a condition of use, inputs from other review disciplines are needed for the final approval of this label update.

## 5.4 Labeling Recommendations (as applicable)

**Error! Reference source not found.** displays the proposed change for *Section 8.4: Pediatric Use* of the current label. Data from the Phase III Study I8B-MC-ITSB have provided statistical evidence to support efficacy of the product, administered via MDI, in treating pediatric patients (1 to 17 years) with T1D.


**Figure 3: Proposed Change for Section 8.4 of the Drug Label**

*Source: proposed uspi by Eli Lilly*

In support of this pediatric indication, a new section on pediatric clinical studies (*Section 14.3 Type 1 Diabetes – Pediatrics*) has been added to Section 14 of the product label. Section 14.3 presents the primary analysis result on HbA1c change from baseline from Study ITSB.

The proposed labelling change is still under review.

# APPENDICES

**Table 11: One-Way Tipping Point Analysis for the Primary Efficacy Results**

| delta | Estimate | SE | LCLMean | UCLMean |
|---|---|---|---|---|
| 0 | -0.01 | 0.07 | -0.16 | 0.14 |
| 0.1 | 0 | 0.07 | -0.15 | 0.14 |
| 0.2 | 0.01 | 0.07 | -0.14 | 0.15 |
| 0.3 | 0.01 | 0.07 | -0.13 | 0.16 |
| 0.4 | 0.02 | 0.07 | -0.13 | 0.17 |
| 0.5 | 0.03 | 0.07 | -0.12 | 0.17 |
| 0.6 | 0.03 | 0.08 | -0.11 | 0.18 |
| 0.7 | 0.04 | 0.08 | -0.11 | 0.19 |
| 0.8 | 0.05 | 0.08 | -0.1 | 0.19 |
| 0.9 | 0.05 | 0.08 | -0.09 | 0.2 |
| 1 | 0.06 | 0.08 | -0.09 | 0.21 |
| 1.1 | 0.07 | 0.08 | -0.08 | 0.22 |
| 1.2 | 0.07 | 0.08 | -0.08 | 0.22 |
| 1.3 | 0.08 | 0.08 | -0.07 | 0.23 |
| 1.4 | 0.09 | 0.08 | -0.06 | 0.24 |
| 1.5 | 0.1 | 0.08 | -0.06 | 0.25 |
| 1.6 | 0.1 | 0.08 | -0.05 | 0.26 |
| 1.7 | 0.11 | 0.08 | -0.05 | 0.26 |
| 1.8 | 0.12 | 0.08 | -0.04 | 0.27 |
| 1.9 | 0.12 | 0.08 | -0.03 | 0.28 |
| 2 | 0.13 | 0.08 | -0.03 | 0.29 |
| 2.1 | 0.14 | 0.08 | -0.02 | 0.3 |
| 2.2 | 0.14 | 0.08 | -0.02 | 0.3 |
| 2.3 | 0.15 | 0.08 | -0.01 | 0.31 |
| 2.4 | 0.16 | 0.08 | 0 | 0.32 |
| 2.5 | 0.16 | 0.08 | 0 | 0.33 |
| 2.6 | 0.17 | 0.08 | 0.01 | 0.34 |
| 2.7 | 0.18 | 0.09 | 0.01 | 0.35 |
| 2.8 | 0.19 | 0.09 | 0.02 | 0.35 |
| 2.9 | 0.19 | 0.09 | 0.02 | 0.36 |
| 3 | 0.2 | 0.09 | 0.03 | 0.37 |
| 3.1 | 0.21 | 0.09 | 0.03 | 0.38 |
| 3.2 | 0.21 | 0.09 | 0.04 | 0.39 |
| 3.3 | 0.22 | 0.09 | 0.04 | 0.4 |
| 3.4 | 0.23 | 0.09 | 0.05 | 0.41 |

Delta is only added to the imputed values for the LY900014 arm

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