I8B-MC-ITSU (b) Statistical Analysis Plan Version: 2.0

Effectiveness of a Basal Rate Reduction With LyumjevTM Versus Humalog® on the Protection From Exercise-Induced Hypoglycemia in Individuals With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion

NCT05262387

Approval Date: 05-Apr-2023

STATISTICAL ANALYSIS PLAN

Effectiveness of a Basal Rate Reduction with Lyumjev™ versus Humalog® on the Protection from Exercise-Induced Hypoglycemia in Individuals with Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Version: 2.0
Statistical Analysis Plan Date: 31-March-2023

Investigational Medicinal Product: LY900014 (Lyumjev)

Protocol Reference: I8B-MC-ITSU
Labcorp Drug Development Study: 8479939

Clinical Phase I

1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

AE	Adverse event
AUC	Area under the plasma concentration versus time curve
AUC(0-15min)	Area under the plasma concentration time curve from time zero to 15 minutes
AUC(0-1h)	Area under the plasma concentration time curve from time zero to 1 hour
AUC(0-30min)	Area under the plasma concentration time curve from time zero to 30 minutes
AUC(0-4h)	Area under the plasma concentration time curve from time zero to 4 hours
AUC(0-∞)	Area under the plasma concentration versus time curve from zero to infinity
AUC(0-t_{last})	Area under the plasma concentration versus time curve from time of suspension to the time of last detectable concentration
CGM	Continuous glucose monitoring
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
early 50% t_{max}	Time to early half-maximal drug concentration
ECG	Electrocardiogram
FFA	Free fatty acids
iAUC	Incremental area under the plasma concentration versus time curve
ICH	International Conference on Harmonisation
IP	Investigational product
late 50% t_{max}	Time to late half-maximal drug concentration
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities

MMTT	Mixed-meal tolerance test
NA	Not applicable
PD	Pharmacodynamic
PG	Plasma Glucose
PK	Pharmacokinetic
RPE	Rating of perceived exertion
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TEAE	Treatment emergent adverse events
TFLs	Tables, Figures, and Listings
t_{last}	Time of the last concentration prior to dose
t_{max}	Time of maximum observed drug concentration
VO_2	Peak oxygen uptake
WHO	World Health Organization
ΔPG1h	Change from baseline 1-hour plasma glucose
ΔPG2h	Change from baseline 2-hour plasma glucose
ΔPGmax	Change from baseline maximum plasma glucose observed during the 4 hours postmeal

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 27 October 2021).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK/PD analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective and Endpoint

The primary objective of the study is:

- To compare changes in plasma glucose (PG) levels with Lyumjev™ versus Humalog® from the start to the end of 60 minutes of moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates, set 60 minutes or 15 minutes before the onset of exercise, respectively.

The primary endpoint of the study is:

- Changes in PG from the start to the end of exercise.

4.2 Secondary Objectives and Endpoints

The secondary objectives of the study are:

- To compare the glucodynamic response with Lyumjev versus Humalog during a dinner mixed-meal tolerance test (MMTT) following moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates, set 60 minutes or 15 minutes before the onset of exercise, respectively
- To compare the PK of insulin lispro between Lyumjev versus Humalog during an MMTT
- To compare the PK of insulin lispro between Lyumjev versus Humalog during 60 minutes of moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates with Lyumjev or Humalog, set 60 minutes or 15 minutes before the onset of exercise, respectively.

The secondary endpoints of the study are:

- Postprandial PG excursion during the test meal (e.g., area under the plasma concentration versus time curve [AUC] from time 0 to 4 hours [AUC{0-4h}])
- Insulin lispro PK during the MMTT after exercise
- Insulin lispro PK during the exercise.

4.3 Exploratory Objectives and Endpoints

The exploratory objectives of the study are:

- To investigate tolerability and safety of Lyumjev and/or Humalog
- To perform an exploratory comparison of glucose variability, time in range, hypoglycemia, and hyperglycemia using continuous glucose monitoring (CGM) profiles obtained from participants receiving Lyumjev and Humalog.

The exploratory endpoints of the study are:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), symptomatic hypoglycemia
- Blood ketone levels
- Overall variability (coefficient of variation [CV] and standard deviation [SD])
- Time in range (70 to 180 mg/dL) during exercise, MMTT assessment, overnight period, and for the entire in-house period
- Time in hypoglycemia (<70 and <54 mg/dL) and hyperglycemia (>180 and 140 mg/dL)
- Mean glucose levels.

5. STUDY DESIGN

Study ITSU will be a single center, randomized, double-blind, 4-period, crossover Williams design exercise and test meal study in physically active adult participants with type 1 diabetes using continuous subcutaneous insulin infusion. The study will consist of 2 active treatment arms, Lyumjev and Humalog. This study will include a screening visit (Visit 1), visits to optimize basal rates (optional based on investigator decision), an assessment day (Visit 2), 4 in-house study periods with study intervention administration (Visits 3, 4, 5, and 6), and a follow-up visit (Visit 7).

Assessment Day (Visit 2)

After screening, all eligible participants will have an assessment day (Visit 2) to undergo a prolonged exercise session at 45% to 55% of predetermined peak oxygen uptake (VO_2) and to determine the insulin bolus dose for the MMTT to be performed in the study.

Participants will be placed on a standardized insulin pump CCI with a new infusion set CCI After disconnecting the participant's own insulin pump, the study pump reservoir will be filled with Humalog by a qualified Clinical Research Unit (CRU) staff. A standard infusion set and catheter will be inserted into the abdominal area, as per the manufacturer's instructions, after the region is inspected for lipodystrophy. The participant's usual basal rate settings will be programmed in the pump and the basal rate infusion will be started.

A standardized lunch will be provided CCI and the bolus insulin dose will be individualized per participant to cover the carbohydrate content. No additional bolus insulin injection should be administered postmeal after lunch prior to the exercise period. The basal rate will be set to a single hourly rate at lunch based on the participant's usual basal rate for this time of day; this will be maintained until the basal rate reduction for the exercise period. A cannula will be inserted for venous access for glucose sampling at around CCI The basal rate in the pump will be reduced by 50% at approximately CCI 1 hour prior to the exercise assessment. A pre-exercise glucose target of CCI will need to be achieved CCI minutes prior to exercise. CCI

Four hours after lunch CCI the participants will be instructed to walk or jog on the treadmill at 45% to 55% of their predetermined peak VO_2 using three 17-minute intervals with two 4-minute and 30-second rest periods in between intervals for a total duration of 1 hour (i.e. CCI). During the exercise period, heart rate will be monitored continuously using a chest strap heart rate monitor, and participants will be asked to rate their perceived exertion using CCI Borg rating of perceived exertion (RPE) scale during the last 2 minutes of each 17-minute interval. Participants will be monitored for safety. If hypoglycemia ensues (plasma or whole blood glucose level CCI the exercise will be terminated, and the participant will be treated with CCI of oral carbohydrates (dextrose tablets). Upon completion of the exercise period, the pump basal rate will be returned to the participant's usual basal rate for this time of the day and this basal rate will be maintained until the end of MMTT.

Participants will be instructed to rest for approximately 30 minutes. A standardized liquid dinner MMTT containing approximately CCI of carbohydrates CCI will be administered approximately CCI hour after the exercise assessment. Participants are expected to complete each test meal within approximately CCI minutes of starting the meal. This meal will be the same as the meals that will be provided during Visits 3 to 6. The dose-finding assessment will use Humalog administered immediately (0 to 2 minutes) before the dinner MMTT using CCI . Selection of bolus dose will be as follows:

- Initial bolus dose selection will be based on discussion between participant and investigator using participant's usual dose requirements or insulin-to-carbohydrate ratio, insulin sensitivity index, and glycemic targets preprogrammed in their personal medical device along with a 25% reduction of the bolus dose to account for increased insulin sensitivity following exercise.
- Postprandial glucose profile over the 4-hour postmeal period will be measured every CCI minutes after administration of proposed insulin dose to verify that the initial bolus dose selected is appropriate using the following:

The selected bolus dose will be used during subsequent liquid dinner MMTT assessments in the study for both Lyumjev and Humalog.

Following completion of glucose sampling, the CCI will be removed and the participant's own insulin pump will be re-introduced using a new infusion set, if necessary, for pump compatibility.

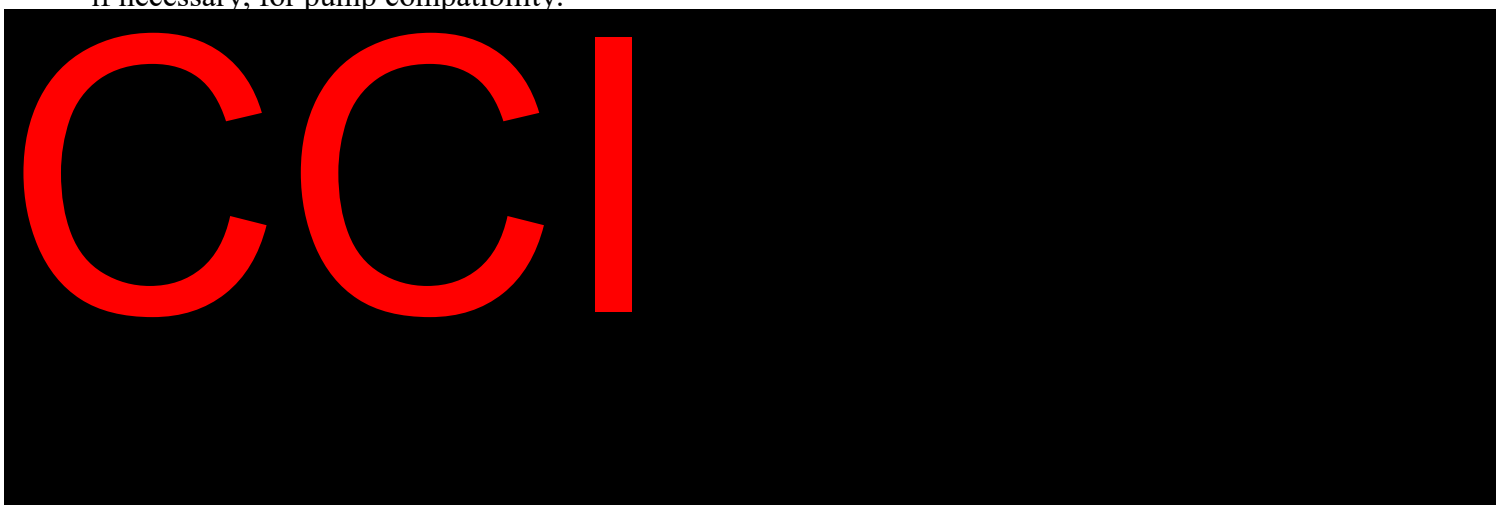

Figure 1: Study activities during Assessment day (Visit 2)

In-house Visits (Visits 3, 4, 5, and 6)

After Visit 2, all eligible participants will undergo 4 in-house study periods (Visits 3 to 6). Each in-house period will comprise a 2-day stay at the CRU. The in-house period will be separated by a washout period of CCI (e.g., between Visit 3, Day 1 and Visit 4, Day 1). Each participant will be randomly assigned to a treatment sequence consisting of 2 treatments (blinded), i.e., Lyumjev and Humalog, and 2 different basal insulin reduction rates to be administered at the 4 separate in-house visits in 4 by 4 crossover Williams design. Randomization will take place on Day -1 of Visit 3.

Upon arrival at the site, participants will be placed on a standardized insulin pump CCI with a new infusion set CCI and a CGM system CCI on the evening before the exercise session CCI

After disconnecting the participant's own insulin pump, the study pump reservoir will be filled with either Lyumjev or Humalog by a qualified CRU staff, and a standard infusion set and catheter will be inserted into the abdominal area, as per the manufacturer's instructions, after the region is inspected for lipodystrophy. The catheter should stay at the same catheter insertion site location for the duration of each period. However, a catheter can be changed to a new location on the abdomen if an occlusion is suspected up to the breakfast meal on Day 1. The participant's usual basal rate settings will be programmed in the pump and the basal rate infusion will be started.

The participants will wear the CRU-provided pump and CGM device during all in-house days. The CGM device will be calibrated on the morning of the exercise day in fasted state, if needed, using the PG values obtained with a glucose analyzer by CRU staff.

A standardized dinner will be provided at approximately CCI On Day 1, a standardized breakfast (CCI) and lunch (CCI) will be provided prior to the scheduled exercise assessment (CCI The insulin dose for these standardized meals (dinner, breakfast, and lunch) before exercise will be individualized per participant to cover the carbohydrate content (including any correction bolus) and will be administered immediately prior (0 to 2 minutes) to the meal using a CCI No additional bolus insulin injection should be administered postmeal after lunch prior to the exercise period. The basal rate will be set to a single hourly rate at lunch CCI based on the participant's usual basal rate for this time of day; this will be maintained until the basal reduction for the exercise period. CCI

A cannula will be inserted for venous access for insulin lispro, glucose, free fatty acids (FFA) and ketones sampling at around CCI Based on the randomization, the pump basal rate will be reduced either 60 minutes or 15 minutes prior to the start of exercise period, scheduled for CCI , in the following manner:

- 50% basal insulin reduction 60 minutes prior to exercise until end of exercise CCI
- 100% basal insulin reduction 15 minutes prior to exercise until end of exercise CCI

Participants will begin the exercise assessment at approximately 4 hours after lunch (approximately 3 PM). They will be instructed to walk or light jog on the treadmill at approximately 45% to 55% of their predetermined peak VO_2 using three 17-minute intervals with two 4-minute and 30-second rest periods in between the intervals for 1 hour. During this period, samples will be collected for glucose, insulin lispro, ketones and FFAs. Heart rate will be monitored, and participants will be asked to rate their perceived exertion using CCI scale during the last 2 minutes of each 17-minute interval, as per the assessment day visit. If hypoglycemia ensues (plasma or whole blood glucose level CCI the exercise will be terminated, and the participant will be treated with CCI of oral dextrose.

Upon completion of the exercise period, the pump basal rate will be returned to the participant's usual rate for this time of the day and this basal rate will be maintained until the end of MMTT. Participants will be instructed to rest for approximately 30 minutes.

A standardized liquid dinner MMTT containing approximately CCI of carbohydrate with a fixed nutrient composition CCI will be administered approximately CCI hour after the exercise assessment. The same individualized insulin bolus dose determined from the dose assessment will be used for both arms (Lyumjev or Humalog) for all 4 in-house visits, unless it is required to be changed to protect participant safety. The insulin bolus dose will be administered immediately prior (0 to 2 minutes) to the meal using a CCI The meal is to be consumed within CCI minutes.

Participants will be without further oral food intake from the start of each test meal to completion of blood collection 4 hours after the start of the meal (approximately 240 minutes) unless required to treat Level 1 hypoglycemia with symptoms or Level 2 hypoglycemia. If a participant's PG concentration rises above CCI for more than CCI hour, insulin glulisine CCI will be administered. In both situations, blood samples for PG (for safety and PD) will be taken, and PK samples will be collected as planned during this period. Following completion of study procedures, the study pump will be disconnected and the CGM system will be removed. The participant's own insulin pump will be re-introduced using a new infusion set, if necessary, for pump compatibility. Participants may leave the CRU at the discretion of the investigator.

Appropriately trained staff must be available until the participants complete the study procedures. The pump can be reused after disinfection, according to the local procedure.

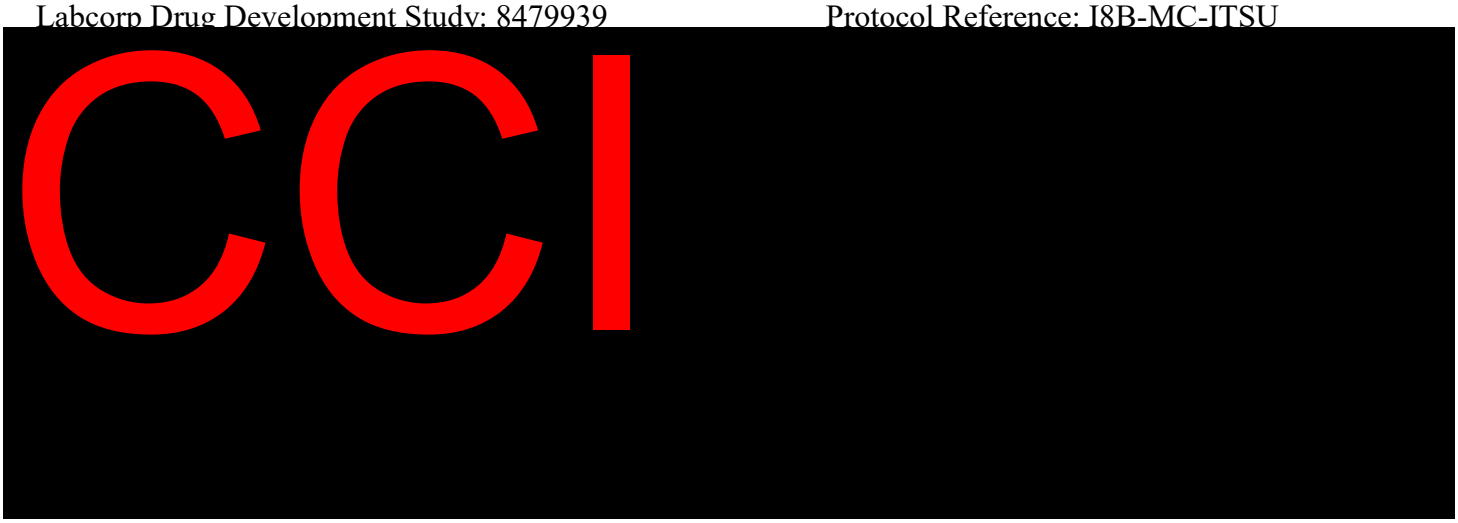

Figure 2: Study activities during in-house periods (Visits 3, 4, 5, and 6)

Treatment	Lyumjev™ or Humalog®	Basal Rate Reduction
A	Lyumjev™	50% 1 hour prior to exercise and to end of exercise
B	Lyumjev™	100% 15 min prior to exercise and to end of exercise
C	Humalog®	50% 1 hour prior to exercise and to end of exercise
D	Humalog®	100% 15 min prior to exercise and to end of exercise

Abbreviations: ED = early discontinuation; R = randomization; T1D = type 1 diabetes mellitus. Randomization on Day -1 of Visit 3 only. Participants will be blinded to study intervention during the in-house periods.

Figure 3: Treatment schedule for in-house study periods (Visits 3 to 6)

6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

Study Treatment Name	Abbreviation	Treatment order in TFL
Lyumjev with 50% basal rate reduction	Treatment A	1
Lyumjev with 100% basal rate reduction	Treatment B	2

Humalog with 50% basal rate reduction	Treatment C	3
Humalog with 100% basal rate reduction	Treatment D	4

The following is a list of the study treatment sequences that will be used in the demographics and vital signs TFLs.

Study Treatment Sequence	Abbreviation	Treatment order in TFL
Treatment A/ Treatment D/ Treatment B/ Treatment C	A/D/B/C	1
Treatment B/ Treatment A/ Treatment C/ Treatment D	B/A/C/D	2
Treatment C/ Treatment B/ Treatment D/ Treatment A	C/B/D/A	3
Treatment D/ Treatment C/ Treatment A/ Treatment B	D/C/A/B	4

7. SAMPLE SIZE JUSTIFICATION

Approximately 32 participants may be enrolled to ensure that at least 28 participants complete the study.

This sample size will provide approximately 80% power to demonstrate a 14-mg/dL difference in the change in PG level from start to the end of the exercise between Lyumjev and Humalog, assuming no true difference in the change in PG level between Lyumjev and Humalog and a SD of 27.9 mg/dL with a 2-sided alpha-level of 0.1. Discontinued participants may be replaced to ensure that 28 participants complete the trial. A replacement participant will be assigned to the same treatment sequence as the participant being replaced.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Safety analysis” population will consist of all participants who are exposed to at least 1 dose of investigational product (IP). Participants will be analyzed according to the intervention they actually received.

The “Full analysis” population will consist of participants who receive at least 1 dose of IP and have completed at least 1 MMTT procedure will be included in the analysis set for the PD analyses. Participants who receive at least 1 dose of insulin during the in-house period and have measurable insulin lispro concentrations will be included in the PK analysis dataset.

The “Modified full analysis” population will consist of all participants who receive both treatments (Lyumjev and Humalog) for at least 1 basal rate reduction (either 50% or 100%) and receive the same dose and meal consumption. Participants who do not keep identical insulin lispro doses for Lyumjev and Humalog or have difference in the consumption of the meal for each visit/period will be excluded from the statistical analysis of the PK and glucodynamic parameters. All participants who receive both treatments with an identical insulin lispro dose for Lyumjev and Humalog will be included for the MMTT PK parameters analysis.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic SD, median, min, max and n; for log-normal data (e.g. the PK parameters: AUCs and maximum observed drug concentration [C_{max}]) the geometric mean and geometric CV% will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, duration of diabetes (years), screening glycated hemoglobin (%), screening C-peptide, smoking & alcohol habits, insulin therapy, VO_2 max, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Parameter Estimation

The PK analyses will be conducted using standard noncompartmental methods of analysis CCI [redacted] on a computer that meets or exceeds the minimum system requirements for these programs. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management.

Free serum insulin lispro concentrations will be used to calculate several PK parameters following the meal bolus for the MMTT, including:

- time to early half-maximal drug concentration (early 50% t_{max}),

- time to late half-maximal drug concentration (late 50% t_{max}),
- maximum observed drug concentration (C_{max}),
- time of maximum observed drug concentration (t_{max}),
- AUC from zero to 15 minutes (AUC[0-15min]),
- AUC from time zero to 30 minutes (AUC[0-30min]),
- AUC from time zero to 1 hour (AUC[0-1h]),
- AUC from time zero to 4 hours (AUC[0-4h]),
- AUC from time zero to infinity (AUC[0-∞]).

Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary. If the prebolus insulin lispro concentrations differ between Lyumjev and Humalog prior to the MMTT, the change from baseline values CCI [redacted] will be used to subtracting the baseline value from all post-dose insulin lispro measurements to calculate the PK parameters. Similarly, the prebolus insulin lispro concentrations differ between Lyumjev and Humalog prior to the lunch before the exercise period, the PK sample collected immediately prior to the bolus will represent as the 0-hour time point for each participant and will be used to subtracting the baseline value from all post-dose insulin lispro measurements to calculate the PK parameters. Other baseline normalization approaches may be explored for assessing the insulin lispro concentrations during the basal reduction. The approach used will be documented in the CSR.

Additionally, an analysis will be conducted to assess the insulin lispro PK during the basal insulin suspension period. PK parameters that were used included the terminal half-life ($t_{1/2}$), time of the last concentration prior to dose (t_{last}) and AUC from time of suspension to the time of the last detectable concentration (AUC[0-t_{last}]). The insulin lispro concentration versus time profile will be compared between Lyumjev and Humalog during this time.

Although attempts will be made to adhere to the scheduled collection times, failure to collect PK samples due to legitimate clinical issues will not be considered as protocol deviations.

Parameters will be individually calculated for each participant based on actual collection times. The mean data will be presented by summary statistics and presented by treatment for those participants who received both treatments (Lyumjev and Humalog) with the same insulin dose (bolus dose for the MMTT or basal reduction) and meal consumption.

PK analysis is the responsibility of Eli Lilly and Company.

9.3.2 Pharmacokinetic Statistical Methodology

The modified full analysis population will be used for these analyses. The PK parameters for the MMTT and during exercise will be analyzed separately.

During the MMTT

Log-transformed PK parameters AUCs, and C_{max} from insulin lispro during the MMTT will be statistically analyzed using a mixed-effect model. The model will include treatment (Lyumjev or

Humalog) and period as fixed effects, and participant as a random effect. The least squares (LS) means will be back-transformed to produce the treatment geometric LS means, ratio of geometric LS means of Lyumjev to Humalog, and corresponding 90% CIs, as well as the p-value, will be reported.

Example of the SAS code is as follows:

```
proc mixed data=xxx;
   class treat period usubjid;
   model logPK = treat period /residual ddfm=kr;
   random usubjid;
   lsmeans treat / cl pdiff alpha=0.1;
   estimate 'Lyumjev vs Humalog' treat 1 -1/ CL alpha=0.1;
   ods output lsmeans=lsm diffs=estims;
run;
```

The same analysis without log transformation will be performed on the PK time parameters (early 50% t_{max}, late 50% t_{max}, and t_{max}) during the MMTT. The treatment LS means, treatment difference in LS means between Lyumjev and Humalog, and corresponding 90% CIs, as well as the 2-sided p-value, will be reported. The treatment ratios and 90% CIs for the ratios will be calculated using the Fieller's theorem[3], see Appendix 2 for further details on this calculation.

Statistical significance will be achieved when the p-value for a test is less than 0.10.

During exercise

A mixed-effects model without log transformation that includes treatment (Lyumjev with 50% basal reduction, Lyumjev with 100% basal reduction, Humalog with 50% basal reduction, and Humalog with 100% basal reduction), sequence, and period as fixed effects and participant-within-sequence as a random effect may be used for the exploratory PK endpoints during the exercise period. LS means, treatment differences in LS means, and the corresponding 90% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LS means will be used to determine statistical significance. The treatment ratios and 90% CIs for the ratios will be calculated using the Fieller's theorem (Chow and Liu 2009).

Additionally, exploratory analysis may be conducted if deemed necessary upon review of the data.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Blood Ketones and Free Fatty Acids

Blood ketones and free fatty acids data will be summarized by timepoint and treatment, and listed.

Glucodynamic Parameter Estimation

Glucodynamic data will be determined from the plasma glucose (PG) reported from the YSI glucose analyzer during the exercise and MMTT assessment.

Glucodynamic data will be analyzed for the participants during each exercise and MMTT assessment. During the exercise period, the change from baseline value (the 0-hour time point prior to the start of exercise) for each participant will be calculated to derive the change in PG level from start to end of exercise.

The rate of PG during the exercise, the nadir PG, decremental AUC, for each exercise assessments will be calculated.

During the MMTT, the change from baseline values CCI [redacted] for each participant will be calculated. The approach used will be documented in the CSR.

The area under the baseline subtracted PG concentration versus time curve (incremental) (iAUC) will be calculated during the MMTT for each in-house periods; the list of derived iAUCs are:

- The incremental AUC from time zero to 30 minutes postmeal (iAUC0-30min)
- The incremental AUC from time zero to 1-hour postmeal (iAUC0-1hour)
- The incremental AUC from time zero to 2-hours postmeal (iAUC0-2hour)
- The incremental AUC from time zero to 3-hours postmeal (iAUC0-3hour)
- The incremental AUC from time zero to 4-hours postmeal (iAUC0-4hour)

In addition, the change from baseline maximum PG observed during the 4 hours postmeal (ΔPGmax) and change from baseline 1-hour plasma glucose (ΔPG1h) and 2-hour plasma glucose after the start of the meal (ΔPG2h) will be calculated. Other partial iAUCs may be calculated, as deemed appropriate.

The mean data will be presented by summary statistics and presented by treatment for those participants who received both treatments (Lyumjev and Humalog) with the same insulin dose (bolus dose for the MMTT or basal reduction) and meal consumption. The data will also be listed.

This will be the responsibility of Eli Lilly and Company.

9.4.2 Pharmacodynamic Statistical Methodology

Primary glucodynamic endpoint

Changes in PG from the start to end of exercise will be statistically analyzed using a mixed–effect model. The model will include treatment (Lyumjev with 50% basal reduction, Lyumjev with 100% basal reduction, Humalog with 50% basal reduction, and Humalog with 100% basal reduction), sequence, period, timepoint, treatment-by-timepoint interaction as fixed effects, and participant-within-sequence as a random effect. Baseline (0 min timepoint) will be included as a covariate. The LS means, difference LS means between Lyumjev and Humalog for corresponding basal rate reduction, and corresponding 90% CIs, as well as the p-value, will be reported.

The p-value on the difference between LS means will be used to determine statistical significance.

Secondary glucodynamic endpoints

For the derived glucodynamic parameters iAUCs ΔPGmax, ΔPG1h, and ΔPG2h, a statistical analysis will be performed during exercise with a basal reduction, and after the MMTT independently. The modified full analysis population will be used for this analysis.

The parameters iAUCs during the MMTT and AUCs during exercise will be log-transformed before the statistical analysis. If negative values occur, the analysis will be performed on untransformed parameters. A mixed effects model will be used for this analysis. The model will include treatment (Lyumjev with 50% basal reduction, Lyumjev with 100% basal reduction, Humalog with 50% basal reduction, and Humalog with 100% basal reduction), sequence, and period as fixed effects, and participant-within-sequence will be included as a random effect. The LS means will be back-transformed to produce geometric means. The treatment geometric LS mean of each treatment, ratio of geometric means between Lyumjev and Humalog for corresponding basal rate reduction, and corresponding 90% CIs will be reported. The p-value will also be reported for the ratios. If the analysis is done on the untransformed parameters, the treatment LS means, difference in LS means between Lyumjev and Humalog for corresponding

basal rate reduction, and corresponding 90% CIs, as well as the p-value, will instead be reported. The treatment ratios and 90% CIs for the ratios will be calculated using the Fieller's theorem.

CCI

The rate of change in PG during exercise period and exploratory GD time parameters will also be statistically analyzed. A mixed effect model will be used, identical to the one above, on the actual values of the parameters. The LS means, difference in LS means between Lyumjev and Humalog for corresponding basal rate reduction, and corresponding 90% CIs, as well as the p-value, will be reported. The treatment ratios and 90% CIs will be reported using Fieller's theorem.

Additionally, exploratory analysis may be conducted if deemed necessary upon review of the data.

9.5 Exploratory PD Analysis

9.5.1 Continuous Glucose Monitoring

Continuous glucose monitoring data will be collected during the exercise, test meal assessments, and overnight periods (Day -1 from CCI on Day 1) as both duration (in minutes and percentage of time in range with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive. The parameters to be derived from the CGM data are:

- duration (in minutes) and percentage of time of hypoglycemia with glucose values <54 and <70 mg/dL (3.0 and 3.9 mmol/L)
- duration (in minutes) and percentage of time of hyperglycemia with glucose values >180 and >250 mg/dL (10.0 and 13.9 mmol/L)
- mean glucose
- overall variability (CV and SD)

The parameters will be summarized by treatment and test period (exercise, test meal, in-house period, or overnight), and listed.

The derived CGM parameters will be statistically analyzed for each test period independently using a mixed-effect model. The modified full analysis population will be used for the analysis. The model will include treatment, sequence, and period as fixed effects, and

participant-within-sequence as a random effect. For the in-house and overnight time periods, the categorical variable treatment will have two levels, Lyumjev and Humalog, whereas the exercise and test meal periods will have four levels, Lyumjev with 50% basal reduction, Lyumjev with 100% basal reduction, Humalog with 50% basal reduction, and Humalog with 100% basal reduction. The LS means, difference LS means between Lyumjev and Humalog for corresponding basal rate reduction (test meal and exercise time periods only), difference in LS means between Lyumjev and Humalog (in-house and overnight time periods only), and corresponding 90% CIs, as well as the p-value, will be reported.

If appropriate, the treatment variable for the in-house time period will be changed to use four factors, using the same factors as the test meal and exercise time periods.

9.5.2 Free Fatty Acids and Ketones

Ketone and FFAs levels will be analyzed for the participants during each exercise and MMTT assessment. The mean data will be presented by summary statistics and presented by treatment for those participants who received both treatments (Lyumjev and Humalog) with the same insulin dose (bolus dose for the MMTT or basal reduction) and meal consumption. The data may be presented graphically. A statistical analysis may be conducted upon review of the data. If a statistical analysis is conducted the same or similar model will be used as presented for the glucodynamic endpoints.

9.6 Safety and Tolerability Assessments

9.6.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A TEAE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

9.6.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose concentrations will be monitored for safety assessments using YSI and CGM (see Section 9.5.9 for further information).

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual blood glucose value, if measured, will be recorded in the CRF, together with any treatments administered. Each category of hypoglycemic events (defined below) will be listed and summarized by treatment. Hypoglycemia is defined as follows:

- **Level 1 hypoglycemia:**

  Glucose CCI
  - Can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

- **Level 2 hypoglycemia:**

  Glucose CCI
  - Also referred to as documented or blood glucose confirmed hypoglycemia with glucose CCI This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

- **Level 3 hypoglycemia:**

  Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

- **Other hypoglycemia:**
  - **Nocturnal hypoglycemia:** A hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep

Investigator's review of glucose results clinically indicative of hypoglycemia will be required.

Participants that are administered and consume carbohydrates during the in-house period will be listed.

9.6.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2021). Concomitant medication will be listed.

9.6.4 Clinical laboratory parameters

Clinical laboratory data are collected at screening only and, with the exception of those reported in the demographics, will not be presented.

9.6.5 Vital signs

Vital signs data will be listed for individual participants.

9.6.6 Electrocardiogram (ECG)

ECGs will be performed for screening and will not be presented.

9.6.7 Perceived Exertion during Exercise

The CCI scale is a well-validated tool[4] to assess perceived physical effort during exercise; it is presented as a scale CCI anchored by verbal descriptors. This scale describes different efforts: CCI is no exertion at all and CCI the maximal exertion or hardest possible effort. Participants will be asked to point to a number that best describes their feelings of the exercise at that moment.

During screening, prospective study participants will have their exercise capacity assessed during a progressive treadmill exercise test until volitional fatigue, as part of the study eligibility. As part of this assessment, the RPE score will be collected every 2 minutes. The data will be listed for those participants who are then enrolled into the study.

During each exercise period, participants will record their perceived physical effort using the RPE score the last 2 minutes of each exercise interval over the 1-hour exercise period. The data will be listed and summarized by assessment day (Visit 2-Humalog) and in-house visit (Visit 3,4,5,6) and by treatment (Lyumjev vs Humalog for the corresponding basal rate reduction).

9.6.8 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

9.6.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd ed. Taylor and Francis Group, LLC; 2009:p 88-90.

CCI

5. September 17, 2020. Accessed October 22, 2021.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	31MAR2023	Update to primary analysis

NA = not applicable

Appendix 2: Supplementary material

To find the CIs associated with the treatment ratio μ_T/μ_R, Fieller's theorem will be used, the equations to calculate the lower and upper interval values as follows:

$$L_{1-\propto/2} = \frac{1}{1-G}\left\{\left(\overline{Y_T}/\overline{Y_R} - G\ S_{RR}/S_{RR}^2\right) - \left[t(\propto/2, n_1+n_2-2)\sqrt{\omega S_{RR}^2}/\overline{Y_R}\ G^*\right]\right\},$$

$$U_{1-\propto/2} = \frac{1}{1-G}\left\{\left(\overline{Y_T}/\overline{Y_R} - G\ S_{RR}/S_{RR}^2\right) + \left[t(\propto/2, n_1+n_2-2)\sqrt{\omega S_{RR}^2}/\overline{Y_R}\ G^*\right]\right\},$$

where

$$G = \left[t(\propto/2, n_1+n_2-2)\right]^2\left(\omega S_{RR}^2/\overline{Y_R^2}\right),$$

$$G^* = \left(\overline{Y_T}/\overline{Y_R}\right)^2 + S_{TT}^2/S_{RR}^2\,(1-G) + S_{TR}/S_{RR}^2\left(G\,S_{TR}/S_{RR}^2 - 2\,\overline{Y_T}/\overline{Y_R}\right),$$

$$\omega = 1/4\,(1/n_1 + 1/n_2),$$

$\overline{Y_R}$ is the LSM estimate of the reference mean, $\overline{Y_T}$ is the LSM estimate of the treatment mean, and t(a,q) is the value of the student's t-distribution pdf at the ath percentile with q degrees of freedom.

Signature Page for VV-CLIN-094317 v1.0

Approval	PPD 31-Mar-2023 16:22:24 GMT+0000

Approval	PPD 03-Apr-2023 09:21:09 GMT+0000

Approval	PPD 05-Apr-2023 03:13:35 GMT+0000

Signature Page for VV-CLIN-094317 v1.0