

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761109Orig1s000

**CLINICAL PHARMACOLOGY
REVIEW(S)**

Office of Clinical Pharmacology Review

BLA Number	761109
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Submission Date	15 Aug 2019
Submission Type	351(a)
Brand Name	LYUMJEV (Proposed)
Generic Name	LY900014 (Insulin Lispro-aabc)
Dosage Form and Strength	<p>LYUMJEV 100 units/mL (U-100) is proposed to be available as:</p> <ul style="list-style-type: none">• 10 mL multiple-dose vial• 3 mL single-patient-use KwikPen®• 3 mL single-patient-use Junior KwikPen®• 3 mL single-patient-use Tempo Pen™• 3 mL single-patient-use cartridges <p>LYUMJEV 200 units/mL (U-200) is proposed to be available as:</p> <ul style="list-style-type: none">• 3 mL single-patient-use KwikPen®
Route of Administration	Subcutaneous injection or intravenous infusion
Proposed Indication	Indicated to improve glycemic control in adults with diabetes mellitus
Applicant	Eli Lilly and Company
Associated IND	IND-127210
OCP Review Team	Suryanarayana Sista, PhD; Liang Li, PhD; Justin Earp, PhD; Manoj Khurana, PhD
OCP Final Signatory	Doanh Tran, PhD

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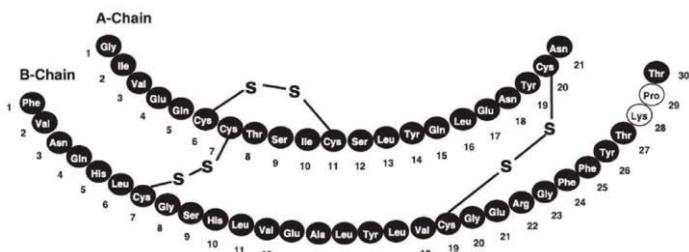
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1. EXECUTIVE SUMMARY

This is an original BLA submitted by Eli Lilly and Company on 15 Aug 2019, seeking marketing approval for LY900014 (Insulin Lispro) injection to improve glycemic control in adults with diabetes mellitus. LY900014 injection is claimed as an ^{(b) (4)} rapid acting insulin lispro, proposed to be marketed under the tradename of LYUMJEV. In this document, the names LY900014 and LYUMJEV are used interchangeably.

Similar to the marketed insulin lispro product, Humalog, LYUMJEV (insulin lispro-aabc injection) is a formulation of a human insulin analog used to lower glucose. LYUMJEV was designed to be absorbed faster than Humalog. Insulin lispro is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin lispro differs from human insulin in that the amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Chemically, it is Lys(B28), Pro(B29) human insulin analog and has the empirical formula C₂₅₇H₃₈₃N₆₅O₇₇S₆ and a molecular weight of 277 5808 Daltons, both identical to that of human insulin. Insulin lispro has the following primary structure:



LYUMJEV is a sterile, aqueous, clear, and colorless solution for subcutaneous or intravenous administration.

The Applicant is positioning that compared to Humalog, the absorption of insulin lispro is faster from LYUMJEV, with a corresponding earlier glucose lowering effect. The pharmacokinetic/pharmacodynamic (PK/PD) differences between LYUMJEV and Humalog were evaluated in healthy subjects as well as in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus T2DM utilizing glucose clamp studies. In addition, meal challenge studies in T1DM and T2DM patients looked at potential PK differences and post-prandial excursion differences between LYUMJEV and Humalog.

Pharmacokinetic findings from these studies indicate that a slightly faster and earlier insulin lispro absorption (early 50% t_{max}) was observed following administration of LYUMJEV, however overall exposure (AUC) did not differ from Humalog. Similarly, glucose infusion rate data showed that there was an earlier glucose-lowering effect with LYUMJEV compared to Humalog, however, overall PD responses (GIR/AUC) did not differ between both products.

In the meal challenge studies, LYUMJEV demonstrated accelerated insulin lispro absorption, reduced late insulin lispro exposure, and shorter exposure duration in T1DM and T2DM patients as compared to Humalog. In T1DM and T2DM patients, when LYUMJEV and Humalog were administered immediately before the start of the meal, LYUMJEV had a greater reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal compared to Humalog. The reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal was not statistically significant when LYUMJEV and Humalog were administered 20 minutes after the start of the meal. Similarly, the postprandial glucose excursion over the 5-hour MMTT was similar between LYUMJEV and Humalog when LYUMJEV was dosed 20 minutes after the start of the meal and Humalog was dosed immediately before the start of the meal.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761109 and found it acceptable to support approval of LYUMJEV in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) population. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The primary evidence of effectiveness for the proposed dosing regimen were obtained from data from 2 efficacy trials, which showed that LYUMJEV, when administered as prandial insulin either immediately before or 20 minutes after the start of the meal in combination with basal insulin, provided effective glycemic control with an acceptable safety profile in patients with T1DM and T2DM.
General dosing instructions	Individualize and adjust the dosage of LYUMJEV based on the patient's metabolic needs, glucose monitoring results, and glycemic control goal. Inject LYUMJEV at the start of a meal subcutaneously into the abdomen, upper arm, thigh, or buttocks. LYUMJEV can be administered within 20 minutes after starting a meal. Intravenous Infusion (LYUMJEV U-100 only): Administration of (b)(4) U-100 must be performed under medical supervision after diluting to concentrations of 0.1 to 1 unit/mL insulin lispro-aabc.
Dosing in patient subgroups	Despite body weight being a significant covariate in the PopPK model, as with all other insulin products, an explicit labeling language of adjustment of LYUMJEV dose based on body weight is not warranted. The general approach of adjusting insulin dose based on the clinical response of the individual includes body weight influence on insulin-glucose homeostasis.
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed formulation is the same as the clinical trial formulation that was used in several clinical pharmacology studies. The to-be-marketed formulation was also used in all the Phase 3 clinical studies, and the 100 units/mL and 200 units/mL bioequivalence study.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Insulin lispro, like other insulins, regulates glucose metabolism through blood glucose lowering by stimulating peripheral glucose uptake into skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also enhances protein synthesis and inhibit lipolysis and proteolysis. LYUMJEV is claimed as an ^{(b) (4)} rapid-acting formulation of insulin lispro developed by the Applicant for subcutaneous (SC) use and for intravenous (IV) use to improve glycemic control in patients with T1DM or T2DM. LYUMJEV is proposed to be made available in 2 dosage strengths: 100 units/mL and 200 units/mL. A summary of the PK and PD characteristics of LYUMJEV is presented below.

The following is a summary of the clinical pharmacokinetics of LYUMJEV:

Absorption:	<ul style="list-style-type: none">Following administration of LYUMJEV, insulin lispro appeared in the circulation within 1 min after injection following a 15 U dose. The early 50% T_{max} (time to 50% maximum insulin lispro concentration) for insulin lispro from LYUMJEV following SC administration is approximately 13 minutes.Insulin lispro exposure with LYUMJEV was similar regardless of injection site.The overall insulin lispro exposure and time of maximum observed drug concentration (T_{max}) was comparable between LYUMJEV and Humalog. From the PK meta-analysis, the median time to maximum insulin lispro (T_{max}) was approximately 1 hour (range 0.17 to 3 hours) after SC administration of LYUMJEV.The amount of insulin lispro that reached the circulation relative to an IV dose (absolute bioavailability) after SC administration of LYUMJEV into the abdomen, deltoid and thigh was approximately 65% in healthy subjects.
Distribution:	<ul style="list-style-type: none">Following IV injection of a 15 U dose of LYUMJEV, the mean (range) volume of distribution (V_z) was 34 L (16 - 53 L).
Elimination:	<ul style="list-style-type: none">Mean (range) clearance of insulin lispro following IV injection of a 15 U dose of LYUMJEV was 32.3 L/h (23.3 - 49.5 L/h), with a mean elimination half-life of 0.73 h (0.47 - 1.23 h)Mean clearance (CL/F) of insulin lispro following SC injection of a 15 U dose of LYUMJEV was 51 L/h (40 – 88 L/h), with a mean half-life of 0.70 h (0.46 – 1.00 h).
Metabolism:	<ul style="list-style-type: none">Human metabolism studies were not conducted for LYUMJEV, since the peptide LYUMJEV is expected to undergo degradation to small peptides and individual amino acids.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed starting dose of LYUMJEV is as follows:

- Individualize and adjust the dosage of LYUMJEV based on the patient's metabolic needs, glucose monitoring results, and glycemic control goal.
- Dosage adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia

- Instruct patients who forget a mealtime dose to monitor their glucose level to decide if an insulin dose is needed, and to resume their usual dosing schedule at the next meal.
- Rotate injection sites to reduce the risk of lipodystrophy

Subcutaneous Injection

- Inject LYUMJEV at the start of a meal subcutaneously into the abdomen, upper arm, thigh, or buttocks.
- LYUMJEV can be administered within 20 minutes after starting a meal.
- LYUMJEV given by subcutaneous injection should generally be used in regimens with intermediate or long-acting insulin.

Intravenous Administration for LYUMJEV U-100 Only

- Do NOT administer LYUMJEV U-200 intravenously.
- Intravenous administration of LYUMJEV U-100 must be performed under medical supervision with close monitoring of glucose and potassium levels to avoid hypoglycemia and hypokalemia
- Dilute LYUMJEV U-100 to concentrations from 0.1 unit/mL to 1.0 unit/mL using 0.9% sodium chloride or 5% dextrose infusion solutions.
- Store diluted LYUMJEV for up to ^(b) (4) days when stored in a refrigerator at 36°F to 46°F (2°C to 8°C) until time of use. The same solution may be stored for up to ^(b) (4) hours at room temperature at 68°F to 77°F (20°C to 25°C).

Converting to LYUMJEV from Other Insulins in Patients with Either Type 1 or Type 2 Diabetes

- If converting from another mealtime insulin to LYUMJEV, the change can be done on a unit-to-unit basis

2.2.2 Therapeutic individualization

Based on findings from individual studies and population PK analyses, other than body weight, no other intrinsic factors affected the PK of insulin lispro after LYUMJEV administration. Dose adjustment of insulin lispro is not required for renal impairment, hepatic impairment, age, body mass index (BMI), gender, other measures of adiposity (waist circumference and skinfold thickness), race, or disease status (T1DM or T2DM). These findings for LYUMJEV are consistent with that of Humalog.

Body weight was identified as a significant covariate on the clearance and volume parameters of the insulin lispro PK. It is well known that the pharmacodynamic response of insulin lispro, as with other insulins, is influenced by body weight. However, dosing for insulin products are based on clinical response and specifically for prandial insulins, meal intake is also taken in consideration. Therefore, an explicit instruction or recommendation of dose adjustment for LYUMJEV based on body weight is not necessary.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following preliminary labeling concepts be included in the final package insert:

Label Section	Acceptable to OCP?			Recommendation
	A	AWE	U	
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	(b) (4)
12.2 Pharmacodynamics	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.2 Pharmacodynamics	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

A = Acceptable; AWE=Acceptable with minor edits; U=Unacceptable/substantive disagreement (must provide comment);

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The clinical development program for LYUMJEV comprised of 32 studies: 22 Phase 1 studies, 1 Phase 2 study, and 9 Phase 3 studies. A total of 8218 subjects participated in these clinical studies, including healthy volunteers (n = 1092), patients with renal impairment (n = 47), patients with hepatic impairment (n = 32) and T2DM patients (n=7047). In addition, clinical pharmacology information from 3 pharmacodynamic studies, 1 absorption, metabolism and elimination study and 1 QTc study for the subcutaneous LYUMJEV were used to support this program. Clinical pharmacology information were obtained from 6 of the 9 Phase 3 studies for LYUMJEV. These studies provide information supporting proof-of-concept as well as the definitive efficacy and safety of LYUMJEV in the target population for the treatment of diabetes.

The regulatory history regarding these communications is summarized below:

Dates	Communication/Meeting Type	Key Communication Points
01 Dec 2015	Type B (Pre-IND) Meeting Written Response	<ul style="list-style-type: none">• Agency's advice to Applicant on characterization of treprostinil and plans to assess immunogenicity
15 May 2017	Type B (End of Phase 2 (EOP2)) Meeting Written Response	<p>Agency's advice to Applicant on the following:</p> <ul style="list-style-type: none">• Conducting a dose-response PK/PD study• Measurement of C-peptide• Bioanalytical strategy• Data submission
27 Aug 2018	Written Response to July 9, 2018, background package	<ul style="list-style-type: none">• Agreement of clinical pharmacology data package.• Agency's caution, that use of meta-analyses for labeling claims will be a review issue• Comments on integrated glucose-insulin (IGI) model
05 Jun 2019	Pre-BLA Meeting Minutes	<ul style="list-style-type: none">• Advice on the submission of studies to support bioequivalence (BE) of U-100 and U-200 formulations of LYUMJEV

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Regulating glucose metabolism is the primary activity of insulins, including insulin lispro. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins enhance protein synthesis and inhibit lipolysis and proteolysis. LYUMJEV is a new formulation of insulin lispro containing [REDACTED] (b) (4) treprostinil and citrate, [REDACTED] (b) (4)
Active Moieties	Insulin lispro
Pharmacodynamics	LYUMJEV generally demonstrated a slightly earlier insulin action while reducing the late insulin action compared to Humalog in studies conducted in healthy subjects and patients with T1DM or T2DM. The onset of insulin action was approximately 10 minutes earlier, and duration of action was 44 minutes shorter following LYUMJEV compared to Humalog. As a result of the earlier insulin action and shorter insulin action duration, a 12% higher maximum glucose infusion rate (R_{max}) was observed with LYUMJEV compared to Humalog. However, the overall glucose infused (G_{tot}) during the clamp between Humalog and LYUMJEV was similar.
General Information	
Bioanalysis	Insulin lispro concentrations in serum were determined using validated enzyme linked immunoassay (ELISA) method, utilizing a biotinylated anti-insulin monoclonal antibody for detection of the captured insulin lispro. Insulin lispro was detected using peroxidase-conjugated purified donkey anti-guinea pig IgG. The validation range was 50 – 2000 pmol/L, with the lower limit of quantification (LLOQ) being 50 pmol/L.
Post Prandial Glucose (PPG) Regimen	During the mixed-meal tolerance test (MMTT) in patients with T1DM or T2DM both LYUMJEV and Humalog reduced PPG when they were given at the start of a meal or 20 minutes after the start of the meal.
C-Peptide Analysis	In studies with healthy subjects and patients with T2DM, the C-peptide response were similar during the euglycemic clamp and the MMTT between LYUMJEV and Humalog.
Effect of Intrinsic Factors on Pharmacokinetics	Except body weight, PopPK analysis did not identify age, gender, and race to have any clinically relevant impact on the PK or PD of LYUMJEV. Body weight was identified as a significant covariate on the clearance and volume parameters of the insulin lispro PK.
Dose Proportionality	Dose proportionality was established for insulin lispro pharmacokinetics across the evaluated LYUMJEV doses of 7 U, 15 U and 30 U. The slope from the statistical analysis showed both the maximum (C_{max}) and total exposure ($AUC_{0-\infty}$) were approximately proportional, as the exponent on dose for C_{max} was 0.96 (95% CI: 0.910 87 to 1.061) and the $AUC_{0-\infty}$ was 1.08 (95% CI: 1.035 to 1.140). Similar to the PK of insulin lispro, the glucose R_{max} and G_{tot} increased with increasing dose following SC injections of LYUMJEV. However, the increase in LYUMJEV dose elicited a statistically less than proportional increase of R_{max} and G_{tot} .
Intra-Subject Variability	<p>PK: The intra-subject variability (CV%) for insulin lispro following SC administration of LYUMJEV were as follows: Healthy subjects - C_{max}: 16%; $AUC_{(0-\infty)}$: 9.5% Patients with T1D or T2D - C_{max}: 18% - 23% $AUC_{(0-\infty)}$: 13%</p> <p>GD: The intra-subject variability (CV%) in healthy subjects for insulin lispro following SC administration of LYUMJEV were as follows: G_{tot}: 27%; R_{max}: 19%</p>
Renal or Hepatic Impairment	Renal and hepatic impairment is not known to impact the pharmacokinetics of insulin lispro. In the presence of renal or hepatic impairment, insulin requirements may be reduced.
Pediatric	LYUMJEV has not been studied in pediatric patients.

Drug-Drug Interaction	No new drug-drug interaction study was carried out with LYUMJEV. As with other insulins, clinically significant drug interactions affecting glycemic response may occur with LYUMJEV. The potential drug-drug interactions for LYUMJEV will be the same as listed for HUMALOG (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020563s196s198s199s199s205747s022s025s026lbl.pdf).
Absorption	
Bioavailability	<p>The bioavailability of insulin lispro relative to an IV dose after SC administration of LYUMJEV into the abdomen, deltoid and thigh was similar regardless of injection site, and was approximately 65% in healthy subjects.</p> <p>In the healthy volunteer study, following SC injection of LYUMJEV into the abdomen, thigh, and deltoid, the mean insulin lispro concentration was detectable up to 7 hours after injection.</p> <p>Compared to Humalog, LYUMJEV had accelerated insulin lispro absorption in both healthy subjects and T1DM and T2DM patients.</p>
T_{max}	LYUMJEV appeared in the circulation within 1 min after subcutaneous injection of a 15 U dose. The time to 50% maximum insulin lispro concentration was 13 minutes, and the time to maximum insulin lispro concentration was achieved at 57 minutes. The overall insulin exposure and time of maximum observed drug concentration (T _{max}) were comparable between LYUMJEV and Humalog.
Bioequivalence of U-200 and U-100	Comparable PK and GIR versus time profiles were observed following administration of 15 U doses of LYUMJEV U-100 and U-200 formulations. The primary PK parameters, C _{max} , AUC _{0-∞} and primary PD parameters G _{tot} and for R _{max} were similar between the U-100 and U-200 formulations. The 90% CIs for all the ratios were contained within the BE limits (0.80, 1.25).
ADME	
Distribution	Findings from Study ITRT indicated that the mean (range) volume of distribution (V _d) following IV injection of a 15 U dose of LYUMJEV was 34 L (16 - 53 L).
Elimination	Findings from Study ITRT indicated that the mean (range) clearance of insulin lispro following IV injection of a 15 U dose of LYUMJEV was 32.3 L/h (23.3 - 49.5 L/h) with a mean (range) elimination half-life of 0.73 hours (0.47 - 1.23 hours). Mean clearance (CL/F) of insulin lispro following SC injection of a 15 U dose of LYUMJEV was approximately 51 L/h (40 – 88 L/h), with a mean half-life of 0.70 h (0.46 – 1.00 h).
Metabolism	The Sponsor did not conduct human metabolism studies with LYUMJEV. The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids.
Excretion	Insulin is a peptide with a molecular weight of approximately ^{(b) (4)} Daltons. Intact insulin is unlikely to be filtered by kidney or excreted in urine.
Immunogenicity	
Incidence	<p>The efficacy or safety of LYUMJEV were not affected by the presence of treatment-emergent antidrug antibodies (TEADAs).</p> <p>The immunogenicity results for LYUMJEV were comparable to Humalog in studies ITRM and ITRN. In Study ITRM with T1DM patients, after 26 weeks of treatment in the open-label and double-blind treatment groups, 32.8% of LYUMJEV-treated and 32.0% of Humalog-treated patients developed TEADA. In this study, after 52 weeks of treatment in the double-blind treatment, 37.3% of LYUMJEV-treated and 34.2% of Humalog-treated patients developed TEADA.</p> <p>In Study ITRN, after 26 weeks of treatment in T2DM patients, 30.7% of LYUMJEV-treated and 23.7% of Humalog-treated patients developed TEADA. Although most patients who developed TEADA had low change in the percent bound tracer divided by total tracer counts (Δ%B/T) values and were cross reactive to native insulin, this did not seem to affect the PK or GD profile of LYUMJEV.</p>

Impact on PK	Approximately 42.5% (918 of 2160) of patients in the Phase 3 and clinical pharmacology studies had antidrug antibody (ADA), likely due to disease state and previous exposure to insulin therapy, including insulin lispro present at baseline. In the population PK analysis, baseline ADA status was one of the covariates identified on insulin lispro clearance however, it explained only about 4.6% of inter-individual variability. The 16.5% increase in insulin lispro clearance observed in patients who were ADA positive at baseline is unlikely to produce any clinical meaningful difference in the PK of LYUMJEV, since insulins are individually titrated. Baseline ADA status did not impact the PK or GD time-action profile of LYUMJEV compared to Humalog.
Impact on Efficacy and Safety	Clinically meaningful association between immunogenicity and drug exposure, efficacy, or risk of adverse events (AEs) were not observed for LYUMJEV.

3.3 Clinical Pharmacology Review Questions

3.3.1 *To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?*

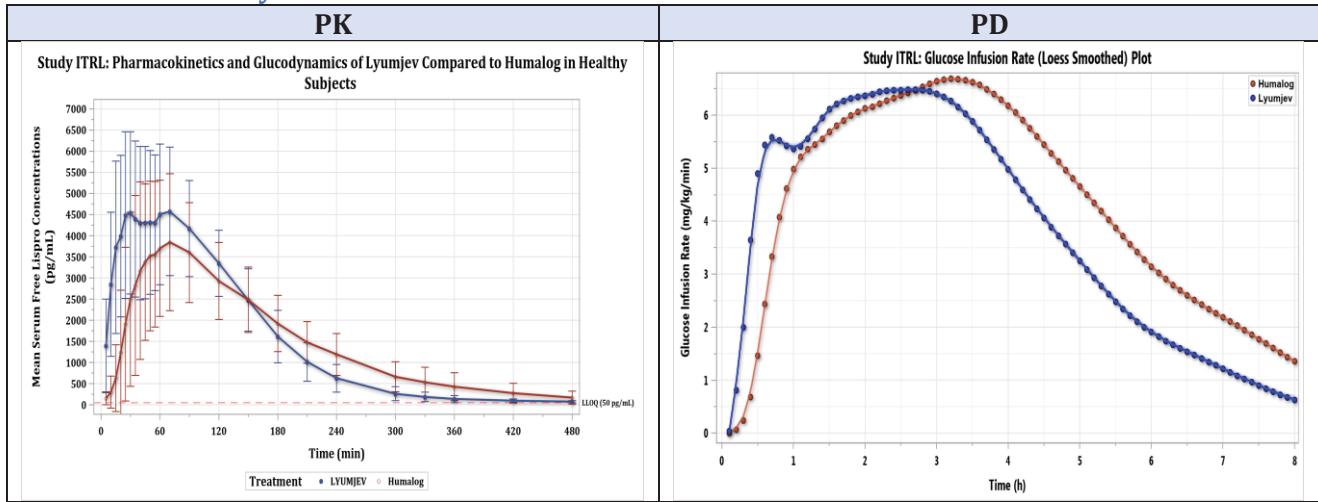
The clinical pharmacology data presented in this NDA provides supportive evidence of effectiveness for LYUMJEV to improve glycemic control in adults with diabetes mellitus. The data from two phase 3 safety/efficacy studies (Studies ITRM and ITRN) provided evidence of effectiveness of LYUMJEV in producing clinically and statistically significant improvements in hemoglobin A1c (HbA1c) (see Clinical review by Dr. Misra in DARRTS).

LYUMJEV contains the same active ingredient, insulin lispro, as Humalog. However, LYUMJEV is claimed by the applicant to have a relatively faster absorption kinetic profile than Humalog without changing its overall exposure to claim a refined time of administration to meal. Accordingly, the data from PK/PD studies (euglycemic clamp and meal-challenge) were reviewed to assess whether the clinical pharmacology data substantiate the applicant's claims on differences in PK and PD response between LYUMJEV and Humalog and their clinical relevance ([Figure 1](#)).

PK/PD of LYUMJEV in comparison to Humalog:

- a. PK/PD data from euglycemic clamp studies showed the following:

Figure 1 Mean Insulin Lispro Concentration (\pm SD) (Left Panel) and Mean Locally Weighted Scatterplot Smoothing Fits of Glucose Infusion Rate (Right Panel) Versus Time by Treatment following 15 U doses of LYUMJEV and Humalog for Study ITRL

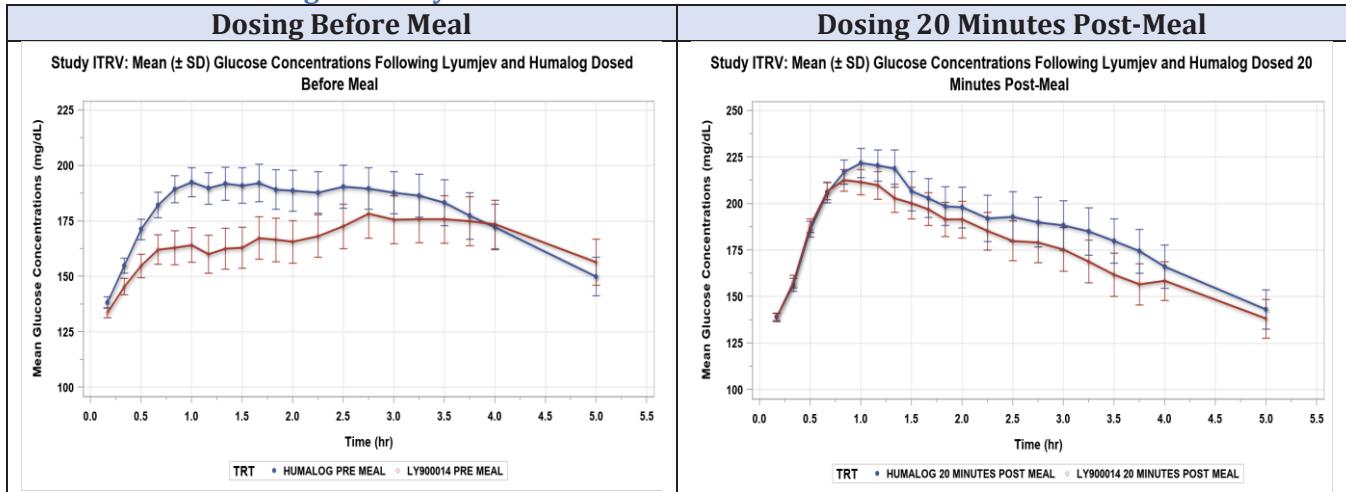


(Source: Reviewer generated graph)

- PK: A slightly faster and earlier insulin lispro absorption (early 50% t_{max}) was observed following administration of LYUMJEV, however overall exposure (AUC) did not differ from Humalog.
- PD: The glucose infusion rate data showed that there was an earlier glucose-lowering effect with LYUMJEV compared to Humalog. However, overall PD responses (GIRAU_C) did not differ between the products.
- The relative differences between LYUMJEV and Humalog were independent of dose as was evident from a rising single dose PK/PD study.
- The relative differences between LYUMJEV and Humalog were evident in subjects with Type 1 diabetes, Type 2 diabetes and did not differ between young and healthy.

PK/PD data from Meal Challenge studies showed the following (Figure 2):

Figure 2 Mean glucose concentration (\pm SE) versus time post meal when dosed immediately before (left) and 20 minutes after the start of the test meal (right) by treatment following a single subcutaneous dose of LYUMJEV or Humalog for Study ITRV



(Source: Reviewer generated graph)

Consistent with the observations from the Euglycemic Clamp PK/PD studies, LYUMJEV demonstrated accelerated insulin lispro absorption, reduced late insulin lispro exposure, and shorter exposure duration in T1DM and T2DM patients as compared to Humalog.

- **T1DM Patients:** When LYUMJEV and Humalog were administered immediately before the start of the meal, LYUMJEV had a greater reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal compared to Humalog. The reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal was not statistically significant when LYUMJEV and Humalog were administered 20 minutes after the start of the meal. Similarly, the postprandial glucose excursion over the 5-hour MMTT was similar between LYUMJEV and Humalog when LYUMJEV was dosed 20 minutes after the start of the meal and Humalog was dosed immediately before the start of the meal.
- **T2DM Patients:** When LYUMJEV and Humalog were administered immediately before the start of the meal, LYUMJEV had a greater reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal compared to Humalog, however the difference was not statistically significant. The reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal was not statistically significant when LYUMJEV and Humalog were administered 20 minutes after the start of the meal. Similarly, the postprandial glucose excursion over the 5-hour MMTT was statistically not significantly different between LYUMJEV and Humalog when LYUMJEV was dosed 20 minutes after the start of the meal and Humalog was dosed immediately before the start of the meal.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed general dosing regimen is appropriate for the general patient population for which the indication is being sought. The suggested dosing for LYUMJEV is same as that for Humalog. However, the proposed time of injection for LYUMJEV at start of the meal or within 20 minutes after starting a meal” in comparison to Humalog (injection within 15 minutes before a meal or immediately after a meal) is supported by data from PK/PD studies (see section 3.3.1) and the Clinical evaluation of this time of injection and doses, which demonstrate that LYUMJEV was noninferior to Humalog on glycemic control in patients with T1DM and T2DM, when administered as prandial insulin per the claimed time of injection, in combination with basal insulin glargine or insulin degludec for 26 weeks (see Clinical and Statistical reviews for further details).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Based on the population PK (PopPK) model, using allometric scaling, baseline body weight was the only covariate retained as a significant covariate on all clearance and volume parameters. Additional predefined patient factors were not required to describe the data. Body weight was identified as a significant covariate on the clearance and volume parameters of the insulin lispro PK. It is well known that the pharmacodynamic response of insulin lispro, as with other insulins, is influenced by body weight. However, dosing for insulin products are based on clinical response and specifically for prandial insulins, meal intake is also taken in consideration. Therefore, an explicit instruction or recommendation of dose adjustment for LYUMJEV based on body weight is not necessary

3.3.4 Are there clinically relevant drug-drug interactions, and what is the appropriate management strategy?

No new drug-drug interaction study was carried out with LYUMJEV. As with other insulins, clinically significant drug interactions affecting glycemic response may occur with LYUMJEV. The potential drug-drug interactions for LYUMJEV will be the same as listed for HUMALOG (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020563s196s198s199,205747s022s025s0261bl.pdf).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How is LYUMJEV identified and what are the analytical methods used to measure them in serum?

Insulin lispro concentrations in serum were determined using validated enzyme linked immunoassay (ELISA) method, utilizing a biotinylated anti-insulin monoclonal antibody for detection of the captured insulin lispro. Insulin lispro was detected using peroxidase-conjugated purified donkey anti-guinea pig IgG. The validation range was 50 – 2000 pmol/L, with the lower limit of quantification (LLOQ) being 50 pmol/L. A summary of validation parameters for the quantitation of free insulin in serum is shown in Table 1.

Table 1 Summary Table of ELISA Method Validation for Quantitation of Free Insulin Lispro (LYUMJEV) in Human Serum

Method ID	Report 3400449
Analyte	Insulin lispro (LY275585)
Matrix	Human serum
Performing Laboratory and Location	(b) (4)
Methodology	ELISA
Extraction Method or Dilution for Immunoassay	3-fold minimum dilution
Validation Range	50.00 to 2000.00 (8.61 to 344.35 pmol/L)
Standard Curve Range	30.00 to 2400.00 pg/mL (5.17 to 413.22 pmol/L) (Standards of 30.00 and 2400.00 were outside the validation range but were added to define the lower and upper portions of the calibration curve)
QC Levels	50.00, 150.00, 400.00 1500.00 and 2000.00 pg/mL
Regression Type and Weighting Factor	4-parameter logistic curve-fit with a 1/Y weighting factor
Validated Dilutions	200000-fold
3400449 Inter-run Accuracy (%RE)	0.1 to 5.7
3400449 Inter-run Precision (%CV)	2.4 to 7.4
3400449 Intra-run Accuracy (%RE)	-6.1 to 10.2
3400449 Intra-run Precision (%CV)	0.3 to 12.5
3400620 Inter-run Accuracy (%RE)	-4.8 to -2.4
3400620 Inter-run Precision (%CV)	2.5 to 4.6
3400620 Intra-run Accuracy (%RE)	-7.9 to 1.4
3400620 Intra-run Precision (%CV)	0.6 to 4.1
3400690 Inter-run Accuracy (%RE)	-13.6 to -0.7 ^a
3400690 Inter-run Precision (%CV)	6.2 to 25.4 ^a
3400690 Intra-run Accuracy (%RE)	-38.3 to 15.5 ^b
3400690 Intra-run Precision (%CV)	0.8 to 83.4 ^b
Ambient Temperature Stability ^c	18 hours at ambient temperature
Refrigerated Stability ^c	18 hours at 4°C
Freeze-thaw Stability	5 freeze-thaw cycles at -80°C
Long-term Frozen Stability	448 days at -20°C 365 days at -80°C
Selectivity Assessment	<u>Selectivity in Normal Human Serum and in Serum from T2M patients:</u> Ten individual human serum samples from healthy subjects, and 10 individual human serum samples from T2M patients. The average recovery in spiked samples met the established method accuracy criteria in both sets of data. The quantification of insulin lispro was not affected in the presence of lipemic serum, nor was any interference observed up to a threshold of 5% hemolysis.

(Source: Module 2.7.1.4 Appendix to the Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table APP.2.7.1.11, pp 26-27

4.2 Biopharmaceutics

LYUMJEV Injection 100 Units/mL (U-100) is a sterile drug product indicated for patients with diabetes mellitus. The unit formula for LYUMJEV Injection U-100 is provided in [Table 2](#), and the unit formula for U-200 is provided in [Table 3](#).

Table 2 Unit Formula of the LYUMJEV U-100 Drug Product

Ingredient	Quantity (per mL)	Function	Reference to Standards
Active Ingredient			
Insulin Lispro	(b) (4) 100 units (b) (4)	Active	USP/Ph.Eur.
Other Ingredients^b			
Treprostil Sodium ^c	1.06 µg	(b) (4)	Non-compendial excipient
Sodium Citrate Dihydrate	4.41 mg		USP-NF/Ph.Eur.
Zinc Oxide ^d	q.s. to provide a Zn ²⁺ content of 39 µg		USP-NF/Ph.Eur.
Magnesium Chloride, Hexahydrate	1.02 mg		USP-NF/Ph.Eur.
Metacresol	3.15 mg		USP-NF/Ph.Eur.
Glycerol	12.1 mg		USP-NF/Ph.Eur.
Hydrochloric Acid Solution	q.s. ^e		See footnote ^e
Sodium Hydroxide Solution	q.s. ^e		See footnote ^e
Water for Injection	q.s. to 1 mL		USP-NF/Ph.Eur.
(b) (4)			

(Source: *Module 3.2.P.1 Description and Composition of U-100 Cartridge, Table 3.2P.1-1, Page 1*)

Table 3 Unit Formula of the LYUMJEV U-200 3 mL Cartridges

Table 3.2.P.1-1 Unit Formula of the LY900014 U-200 3 mL Cartridges

Ingredient	Quantity (per mL)	Function	Reference to Standards
Active Ingredient			
Insulin Lispro	(b) (4) 200 units (b) (4)	Active	USP/Ph.Eur.
Other Ingredients^b			
Treprostinil Sodium ^c	1.06 µg	(b) (4)	Non-compendial excipient
Sodium Citrate Dihydrate	4.41 mg		USP-NF/Ph.Eur.
Zinc Oxide ^d	q.s. to provide a Zn ²⁺ content of 52 µg		USP-NF/Ph.Eur.
Magnesium Chloride, Hexahydrate	1.02 mg		USP-NF/Ph.Eur.
Metacresol	3.15 mg		USP-NF/Ph.Eur.
Glycerol	12.1 mg		USP-NF/Ph.Eur.
Hydrochloric Acid Solution	q.s*		See footnote*
Sodium Hydroxide Solution	q.s*		See footnote*
Water for Injection	q.s. to 1 mL		USP-NF/Ph.Eur.
(b) (4)			

(Source: Module 3.2.P.1 Description and Composition of U-200 Cartridge, Table 3.2P.1-1, Page 1)

4.2.1 What is the role of treprostinil, and sodium citrate used in the formulation for LYUMJEV?

Treprostinil (Remodulin) is a prostacyclin analogue, approved to be administered either as an intravenous infusion or an SC infusion for the treatment of symptomatic pulmonary arterial hypertension (PAH). (b) (4)

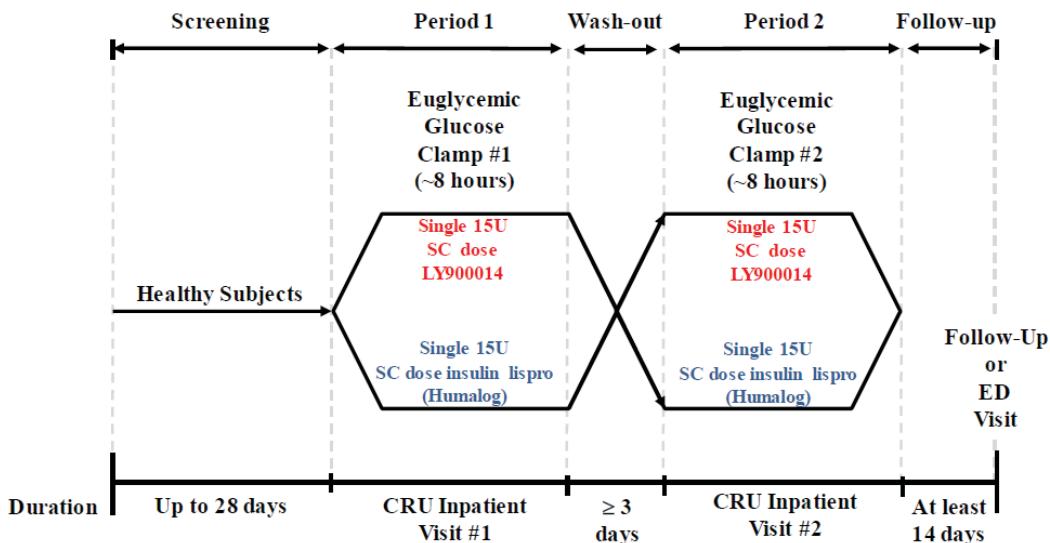
treprostinil was used in micro-doses (1 µg/mL treprostinil / (100 U/mL) insulin dose) in the formulation and at the levels used were not quantifiable in blood.

(b) (4)

4.3 Clinical PK and PD Assessments

Study ITRL: PK/PD differences between LYUMJEV and Humalog in healthy subjects

Comparison of the PK and GD of insulin lispro following a single, 15 U SC dose of LYUMJEV with the PK and GD of a single, 15 U SC dose of insulin lispro (Humalog) was carried out in a Phase 1, single-center, randomized, subject- and investigator-blind, 2-treatment, 2-period, crossover study in healthy subjects. A total of 32 healthy Asian subjects, 29 males and 3 females, aged between 22 and 60 years (mean = 39 years), participated in this study. The mean body weight of the population was 66.5 kg and the mean BMI was 23.3 kg/m². A schematic of the study design is shown below:



Abbreviations: CRU = clinical research unit; ED = early discontinuation; SC = subcutaneous; U= unit.

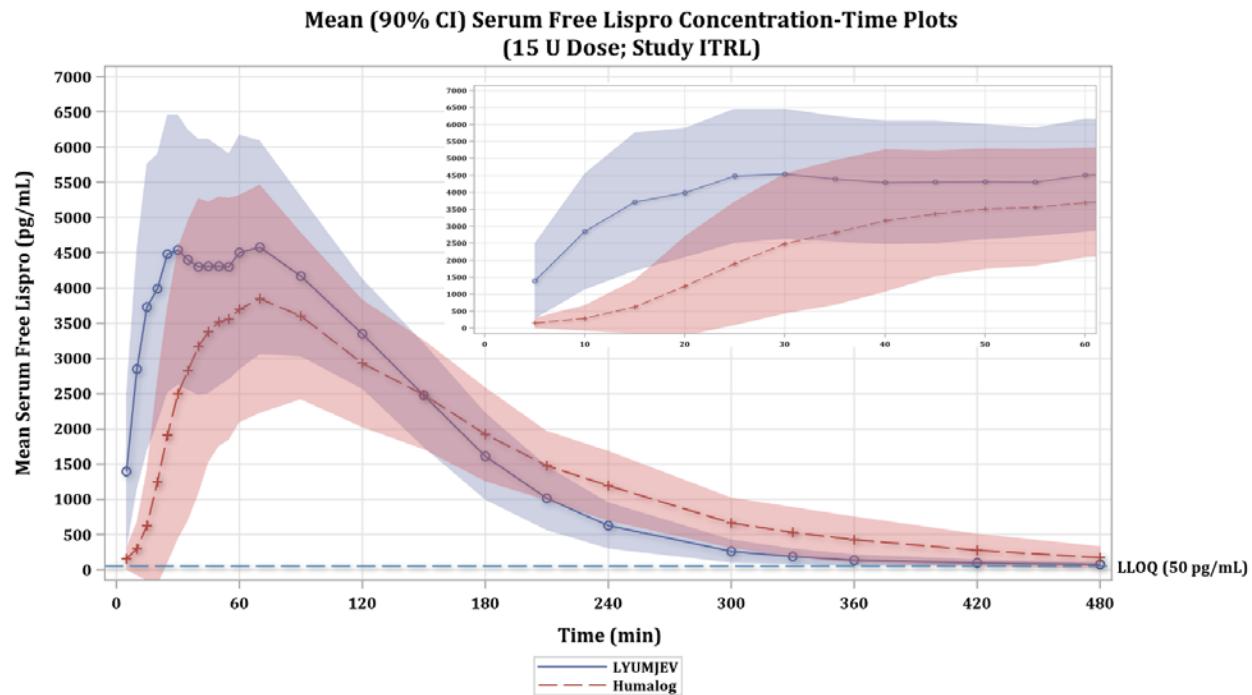
A manual 8-hour glucose clamp was used in the study. The aim of the euglycemic glucose clamp was to maintain target glucose levels constant through infusion of a 20% D-glucose (dextrose) solution after the administration of a dose of insulin. Blood glucose was measured approximately every 2.5 minutes for the first 30 minutes during the clamp, then every 5 minutes until 120 minutes post-dose, and subsequently every 10 minutes until 480 minutes post-dose. The glucose infusion rate (GIR) was adjusted manually to maintain a predetermined target blood glucose concentration for the individual subject. Thus, blood glucose concentrations were kept constant while the GIR varied. The varying GIR reflected the GD activity of insulin.

The target value for blood glucose concentrations was defined as 5 mg/dL below the mean of pre-dose fasting blood glucose concentrations. The baseline mean was calculated from either 3 or 4 pre-dose glucose measurements. The minimum glucose target for an individual clamp was ≥ 63 mg/dL (whole blood).

Serial blood samples were taken for the PK measurement of insulin lispro.

The pharmacokinetics of insulin lispro and the glucodynamics during a euglycemic clamp following administration of a 15 U single subcutaneous (SC) dose of LYUMJEV and insulin lispro (Humalog) was evaluated in healthy subjects. The mean insulin lispro exposure following administration of single 15 U doses of LYUMJEV and insulin lispro (Humalog) is presented in [Figure 3](#).

Figure 3 Mean insulin lispro concentration (90% C.I) versus time for the duration of the clamp (inset - for the first hour) by treatment following 15 U doses of LYUMJEV and Humalog



(Source: Reviewer generated graph)

Pharmacokinetics:

Following doses of 15 U LYUMJEV or HUMALOG, faster, earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ (Figure 3, Table 4). Early 50% T_{max} for insulin lispro was reduced from 30.7 minutes to 10.8 minutes (~65%) following LYUMJEV administration compared to Humalog (Table 4). There were corresponding increases in $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 4.61- and 1.99-fold, respectively, and a significantly higher C_{max} after LYUMJEV administration compared to Humalog (Table 4).

There was a 46.5-minute mean (~24%) reduction in late 50% T_{max} for LYUMJEV compared to Humalog (Table 4). There was a corresponding 31% late insulin lispro exposure $AUC_{(2-8h)}$ reduction for LYUMJEV compared to Humalog (Table 4).

However, the overall insulin exposure $AUC_{(0-\infty)}$ was not significantly different between LYUMJEV and Humalog (Table 4).

Table 4 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog

Parameter	Treatment	N	Geometric Least squares means	Ratio of geometric least squares means Test : Reference	90% CI for the ratio (Lower, Upper)	P-value		
Cmax (pmol/L)	15 U Humalog	32	692					
	15 U LY900014	30	883	1.28	(1.17, 1.39)	<.0001		
AUC(0-inf) (pmol.h/L)	15 U Humalog	32	1989					
	15 U LY900014	31	2055	1.03	(0.986, 1.08)	0.2494		
Parameter	Treatment	N	LS means	Difference in LS means (Test - Reference)	90% CI for the difference (Lower, Upper)	Ratio of LS means (Test : Reference)	90% CI for the ratio (Lower, Upper)	
early 50% tmax (min)	15 U Humalog	32	30.7	-19.9	(-22.4, -17.4)	<.0001	0.352	(0.312, 0.395)
	15 U LY900014	30	10.8					
tmax (h)	15 U Humalog	32	1.24	-0.188	(-0.367, -0.010)	0.0832	0.848	(0.722, 0.988)
	15 U LY900014	31	1.06					
late 50% tmax (min)	15 U Humalog	32	197	-46.5	(-61.7, -31.3)	<.0001	0.765	(0.711, 0.826)
	15 U LY900014	31	151					
t1/2 (h)	15 U Humalog	32	1.16	-0.240	(-0.386, -0.093)	0.0093	0.794	(0.697, 0.909)
	15 U LY900014	31	0.921					

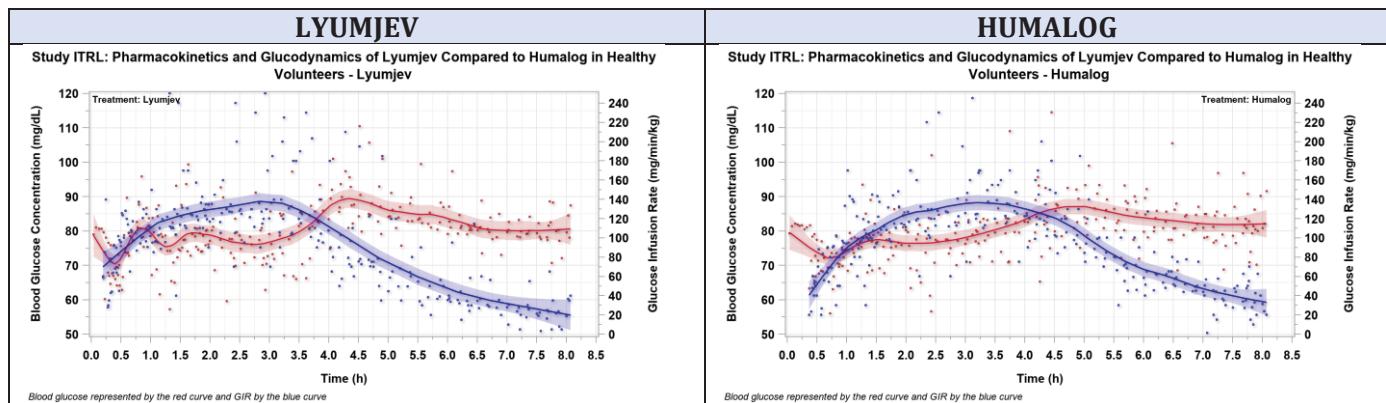
The CIs for the ratio were calculated using the Fieller's theorem.
P-value is for the test of the mean difference.
Model: PK = Sequence + Period + Treatment + Subject + Random Error, where Patient is fitted as a random effect
Abbreviations: CI = Confidence Interval; LS = Least squares; N = Number of patients
0.1 Significance level

(Source: CSR for Study ITRL, Tables ITRL.7.2 and ITRL.7.3, Pp 23-24)

Pharmacodynamics:

Individual blood glucose concentrations and GIR versus time and mean LOESS fits comparing a 15 U dose of LYUMJEV to 15 U Humalog are presented in [Figure 4](#).

Figure 4 Individual and Mean Blood Glucose Concentration and Glucose infusion Rate Following 15 U Doses of LYUMJEV or Humalog



(Source: Reviewer generated graph)

A slightly greater insulin onset of action within the first hour after dose administration was observed following LYUMJEV administration compared to Humalog ([Figure 4](#)). There were corresponding 13.8- and 2.21-fold increases in the total amount of glucose infused $G_{\text{tot}(0-30\text{min})}$ and $G_{\text{tot}(0-1\text{h})}$, respectively, following LYUMJEV compared to Humalog ([Table 5](#)). There was a 41% reduction in time to onset of insulin action (T_{onset}) and 47% reduction in early 50% time to maximum glucose infusion rate (tR_{max}) after LYUMJEV administration compared to Humalog ([Table 5](#)). A slightly lower G_{tot} was observed following

LYUMJEV compared to Humalog. There was no statistically significant difference between treatments in the maximum glucose infusion rate, R_{\max} (Table 5).

Table 5 Pharmacodynamic Parameters and Statistical Analysis after Administration of 15 U of LYUMJEV Compared to 15 U Humalog

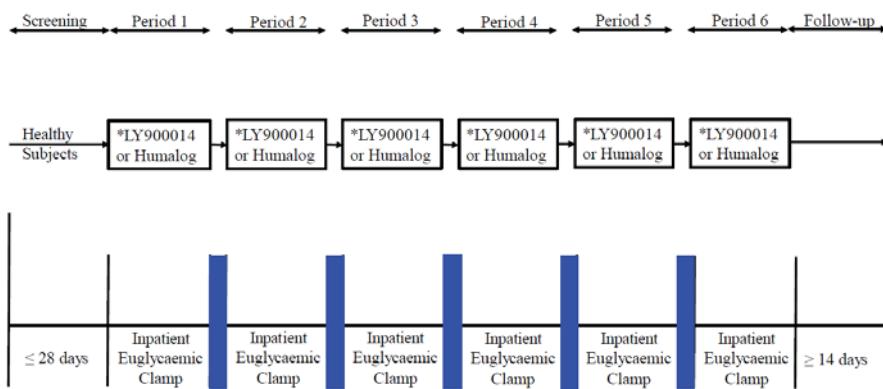
Parameter	Treatment	N	Geometric Least squares means	Ratio of geometric least squares means Test : Reference	90% CI for the ratio (Lower, Upper)	P-value
Rmax (mg/min)	15 U Humalog 15 U LY900014	32 32	460.14 462.89	1.01	(0.94, 1.08)	0.887
Gtot (mg)	15 U Humalog 15 U LY900014	32 32	125414.28 115047.58	0.92	(0.85, 0.99)	0.072
Parameter	Treatment	N	LS means	Difference in LS means (Test - Reference)	90% CI for the difference (Lower, Upper)	Ratio of LS means (Test : Reference) P-value
Tonset (min)	15 U Humalog 15 U LY900014	32 32	33.97 20.10	-13.88	(-15.85, -11.90)	<.0001 0.59
tRmax (min)	15 U Humalog 15 U LY900014	32 32	170.81 131.25	-39.56	(-62.70, -16.43)	0.0069 0.77
early 50% tmax (min)	15 U Humalog 15 U LY900014	32 32	55.07 29.33	-25.75	(-33.20, -18.29)	<.0001 0.53
late 50% tmax (min)	15 U Humalog 15 U LY900014	31 32	335.84 273.67	-62.18	(-77.73, -46.62)	<.0001 0.81

The CIs for the ratio were calculated using the Fieller's theorem.
P-value is for the test of the mean difference.
Model: GD = Sequence + Period + Treatment + Subject + Random Error, where Patient is fitted as a random effect
Abbreviations: CI = Confidence Interval; LS = Least squares; N = Number of patients
0.1 Significance level

(Source: CSR for Study ITRL, Tables ITRL.7.5 and ITRL.7.6, Pp 28-29)

Study ITSH: Dose-proportionality of Lyumjev and Humalog when administered subcutaneously in healthy subjects

Dose proportionality of the 3 dose levels of LYUMJEV as assessed by insulin lispro PK and GD measures following SC doses of 7, 15, and 30 U of LYUMJEV compared to Humalog was carried out in a Phase 1, randomized, subject- and investigator-blind, 6-period complete crossover study in up to 42 healthy subjects. A total of 42 healthy subjects (40 White, 2 American Indian or Alaska Native), 27 males and 15 females, aged between 18 and 60 years (mean = 42 years), participated in this study. The mean body weight of the population was 77.1 kg and the mean BMI was 24.8 kg/m². Thirty-nine of the 42 enrolled subjects completed the study. A schematic of the study design is shown below:



*Single dose of 7, 15, or 30 U of LY900014 or Humalog administered subcutaneously to the abdomen. Euglycaemic clamp procedure after each dose.

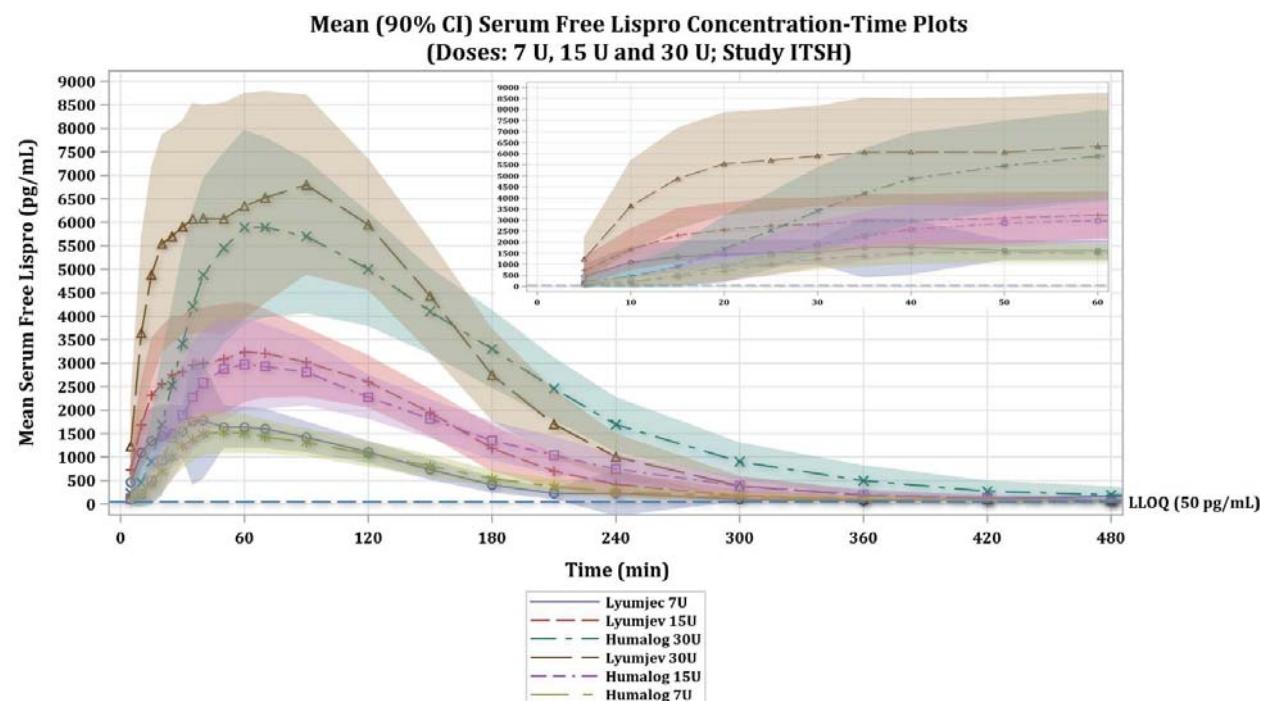
An automated glucose clamp was used in the study. At least 30 minutes before the planned administration of study drug, subjects were connected to an automated clamp device (ClampArt®) for continuous blood glucose monitoring to determine their baseline blood glucose level. Baseline was established as the mean of blood glucose concentrations at -6, -4, and -2 minutes prior to study drug administration. After study drug administration, onset of action (as measured by ClampArt) occurred when blood glucose dropped 5 mg/dL (0.3 mmol/L) from baseline. This blood glucose level 5 mg/dL below baseline was used as the euglycemic glucose clamp target level throughout the remainder of the clamp procedure.

Glucodynamic analyses were conducted on those subjects who completed at least 1 clamp procedure.

Serial blood samples were taken for the PK measurement of insulin lispro.

The mean insulin lispro exposure following administration of single doses of 7 U, 15 U and 30 U LYUMJEV and insulin lispro (Humalog) is presented in [Figure 5](#).

Figure 5 Mean insulin lispro concentration (90% C.I) versus time for the duration of the clamp (inset - for the first hour) by treatment following 15 U doses of LYUMJEV and Humalog



(Source: Reviewer generated graph)

Pharmacokinetics:

Following doses of 7, 15 or 30 U LYUMJEV or HUMALOG, faster, a 2.13- to 4.61-minute earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-15min)}$, $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ ([Figure 5, Table 6](#)). Early 50% T_{max} for insulin lispro was reduced by approximately 51%, 51% and 55% following 7, 15 and 30 U LYUMJEV administration, respectively, compared to the same doses of Humalog ([Table 6](#)). There were corresponding increases in $AUC_{(0-15min)}$, $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 6- to 7.9-fold, 2.3- to

3.6 fold, and 1.3- to 1.63-fold, respectively, and a 13% to 19) higher C_{\max} across the dose range after LYUMJEV administration compared to Humalog (Table 6).

Compared to Humalog, late insulin lispro exposure was reduced with LYUMJEV as measured by a 22% to 29% reduction in the $AUC_{(2-10h)}$, and a 45% to 52% reduction in $AUC_{(3-10h)}$ (Table 6). The duration of insulin lispro in the serum was reduced by 70 minutes for the 7 U dose, 67 minutes for the 15 U dose, and 86 minutes for the 30 U dose following LYUMJEV administration compared to Humalog. (Table 6).

Table 6 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 7, 15 or 30 U of LYUMJEV Compared to 7, 15 or 30 U of Humalog

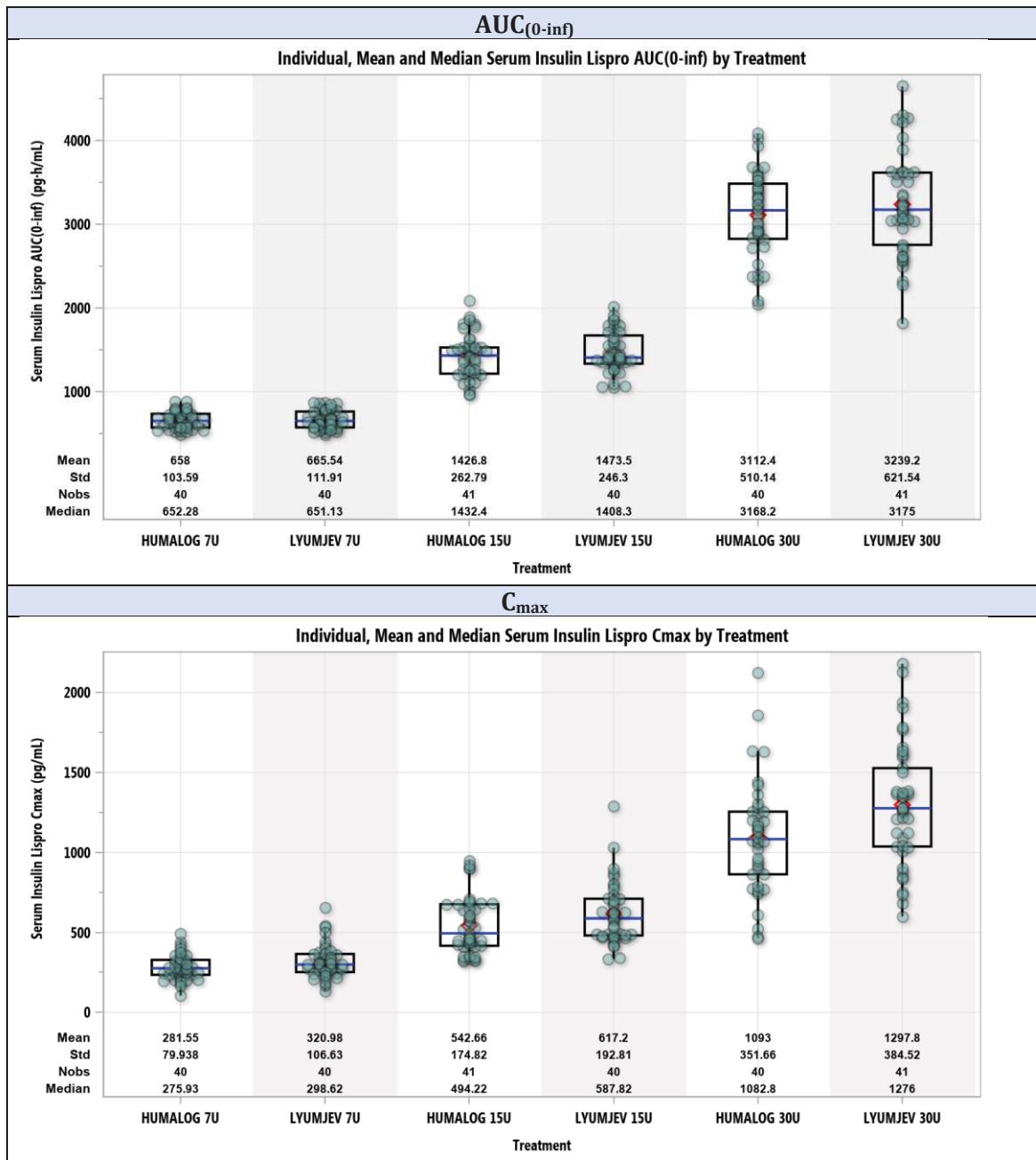
Parameter	Treatment	N	Geometric LSmeans	Ratio of geometric LSmeans (LY900014 vs Humalog)	95% CI for the ratio (Lower, Upper)	P-value
C_{\max} (pmol/L)	7 U Humalog SC	40	270			
	7 U LY900014 SC	40	305	1.13	(1.05, 1.21)	0.0011
	15 U Humalog SC	41	521			
	15 U LY900014 SC	40	588	1.13	(1.05, 1.22)	0.0010
	30 U Humalog SC	40	1036			
	30 U LY900014 SC	41	1232	1.19	(1.11, 1.28)	<.0001
$AUC(0-\infty)$ (pmol.h/L)	7 U Humalog SC	40	649			
	7 U LY900014 SC	40	655	1.01	(0.973, 1.05)	0.6089
	15 U Humalog SC	41	1412			
	15 U LY900014 SC	40	1441	1.02	(0.983, 1.06)	0.2883
	30 U Humalog SC	40	3064			
	30 U LY900014 SC	41	3156	1.03	(0.992, 1.07)	0.1244
$AUC(0-t_{last})$ (pmol.h/L)	7 U Humalog SC	40	630			
	7 U LY900014 SC	40	641	1.02	(0.979, 1.06)	0.3855
	15 U Humalog SC	41	1392			
	15 U LY900014 SC	40	1427	1.03	(0.987, 1.07)	0.1930
	30 U Humalog SC	40	3037			
	30 U LY900014 SC	41	3139	1.03	(0.995, 1.07)	0.0895

(Source: CSR for Study ITSH, Table ITSH.7.2 Page 28-29)

Dose Proportionality:

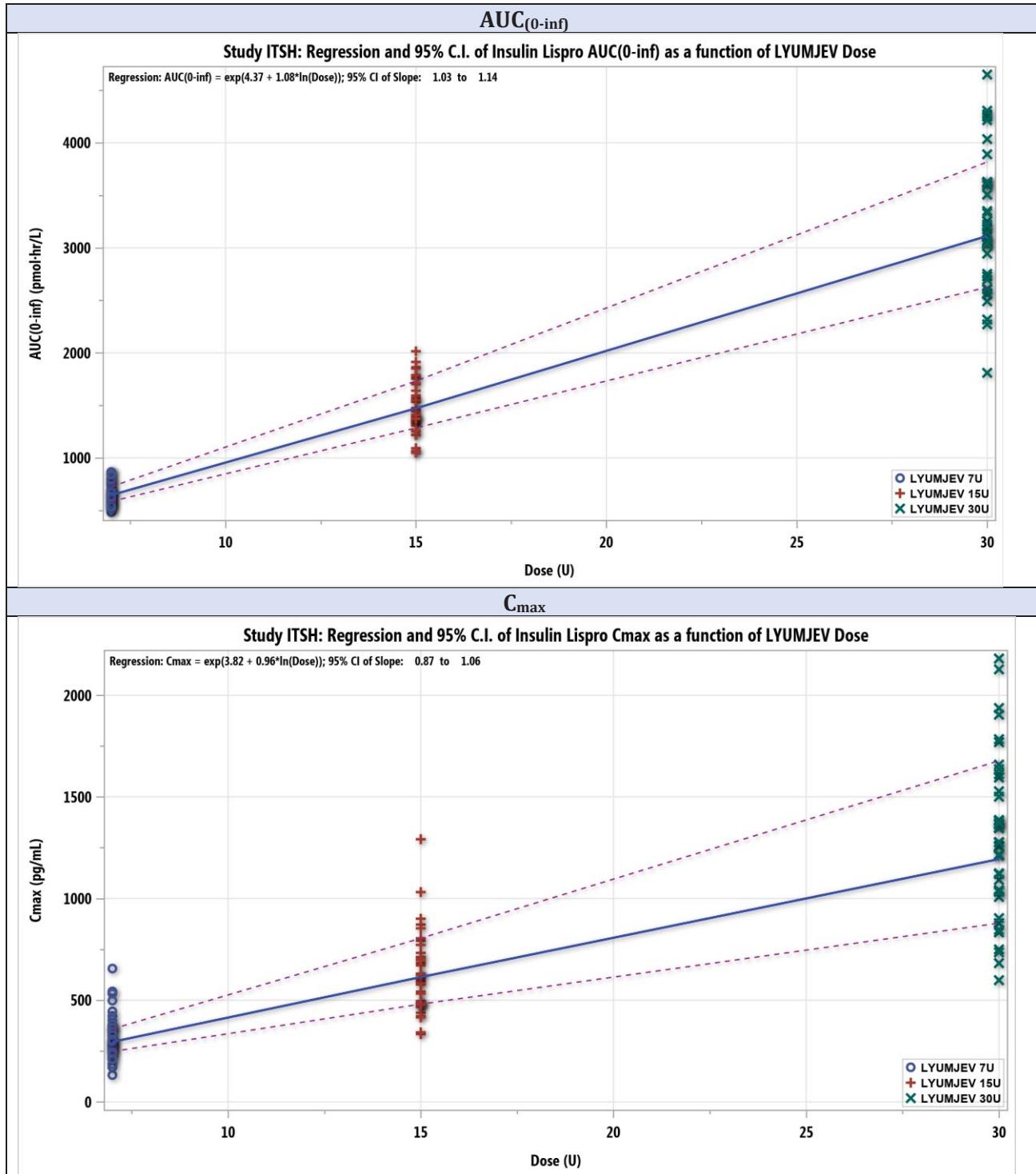
Insulin lispro exposure ($AUC_{(0-\infty)}$ and C_{\max}) following administration of LYUMJEV or Humalog shows an increase by dose (Figure 6). Dose proportionality of the 3 doses of LYUMJEV used in the study was assessed by a power-model regression analysis of $AUC_{(0-\infty)}$ or C_{\max} as a function of dose. The exponents for the insulin lispro C_{\max} and $AUC_{(0-\infty)}$ across the dose range of 7 to 30 U were 0.96 (95% CI: 0.87 to 1.06) and 1.08 (95% CI: 1.03 to 1.14), respectively (Figure 7).

Figure 6 Insulin Lispro PK Parameters as a Function of Dose Following 7, 15 and 30 U Doses of LYUMJEV or Humalog



(Source: Reviewer generated graph)

Figure 7 **Regression of PK Parameters as a Function of Dose Following 7, 15 and 30 U Doses of LYUMJEV**

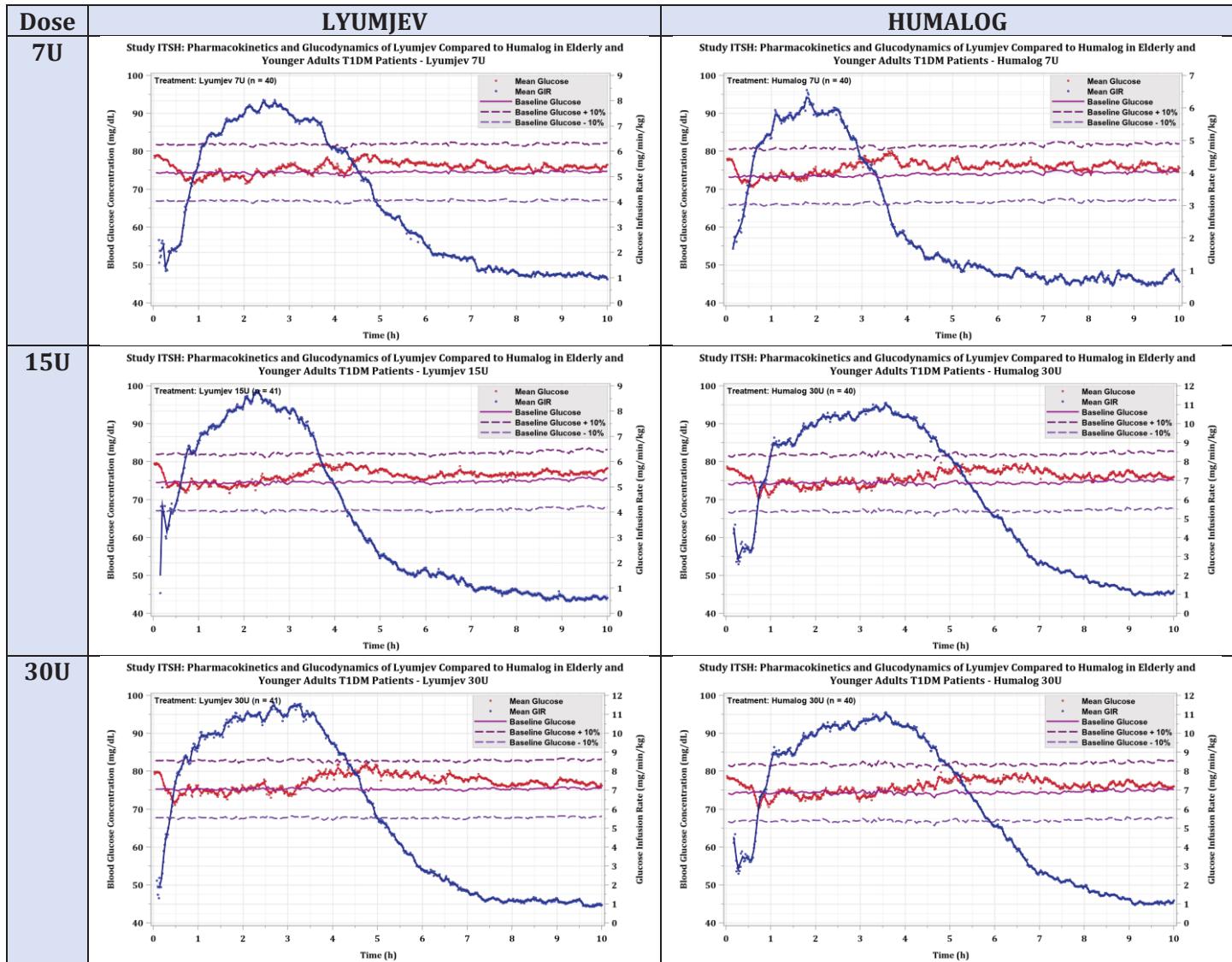


(Source: Reviewer generated graph)

Pharmacodynamics:

Mean blood glucose concentrations and GIR versus time and mean LOESS fits comparing 7, 15 and 30 U doses of LYUMJEV to 7, 15 and 30 U doses of Humalog are presented in [Figure 8](#).

Figure 8 Individual and Mean Blood Glucose Concentration and Glucose infusion Rate Following 7, 15 and 30 U Doses of LYUMJEV or Humalog



(Source: Reviewer generated graph)

A slightly greater insulin onset of action and shorter duration was observed following LYUMJEV administration compared to Humalog ([Figure 8](#)). Across the 7, 15 and 30 U dose range, the onset of the insulin action (T_{onset}) was reduced by 7.13- to 9.23-minutes (reduction of 29% to 35%) for LYUMJEV compared to Humalog. There were corresponding 2.51- to 3.21-fold, 1.63- to 1.85-fold and 1.23- to 1.34-fold increases in the total amount of glucose infused $G_{tot(0-30min)}$, $G_{tot(0-1h)}$ and $G_{tot(0-2h)}$, respectively, following LYUMJEV compared to Humalog.

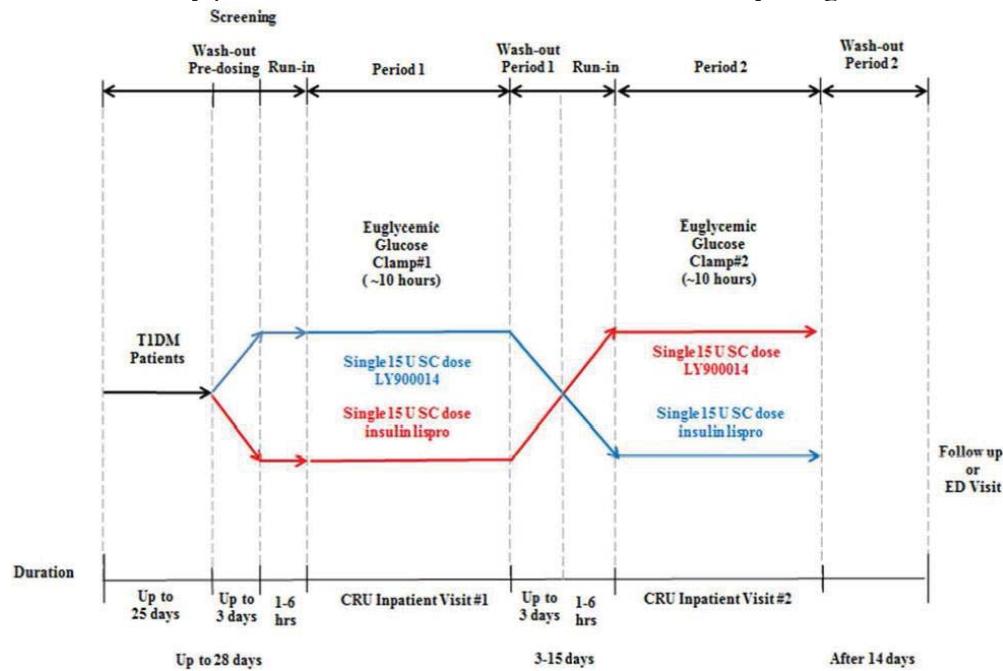
There was a 31.42- to 58.37-minute difference in the late 50% tR_{max} reduction following administration of LYUMJEV compared to Humalog across the dose range. Compared to Humalog, following LYUMJEV

administration glucose infused from 2, 3 and 4 hours to the end of the clamp, $G_{tot(2h-End)}$, $G_{tot(3h-End)}$ and $G_{tot(4h-End)}$ were reduced by 17% to 25%, 22% to 32%, and 32% to 45%, respectively, across the dose range. There was a shorter duration of action of 67, 47 and 51 minutes for the 7 U, 15 U and 30 U doses following LYUMJEV compared to Humalog. Total glucose infused over the clamp duration (G_{tot}) were similar between the treatments. The time to maximum glucose infusion rate, tR_{max} was 27 minutes earlier for LYUMJEV compared to Humalog following a 15 U dose but was not significantly different for either the 7 or 30 U doses.

Study ITRR – PK/PD of LYUMJEV versus Humalog in younger adult and elderly patients with T1DM

Study ITRR was a Phase 1, randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study that compared the PK and GD of insulin lispro following a bolus administration of a single 15-U dose through SC injection of either LYUMJEV or Humalog in elderly and younger adult patients with T1DM who were receiving insulin either through multiple daily insulin injections or through continuous subcutaneous insulin infusion (CSII).

A total of 80 White patients with T1DM, 39 elderly patients and 41 young adult patients aged between 22-45 years (mean = 32 years) for young adults and 65-77 years (mean = 68.5 years) for elderly patients, participated in this study. The mean body weights of young adults and elderly patients were 78.4 kg and 76.7 kg, respectively; the mean BMI of young adults and elderly patients were 24.8 kg/m^2 and 26.2 kg/m^2 , respectively. Of the young adult patients, 28 were female and 13 were male while 22 of the elderly patients were male while 17 elderly patients were female. A schematic of the study design is shown below:



An automated glucose clamp (ClampArt) was used in the study to maintain a target glucose level through infusion of a 20% D-glucose (dextrose) solution after the administration of a dose of insulin. A 1- to 6-hour run-in period was conducted to stabilize the patients' blood glucose level through the use of a variable infusion of either glucose or insulin glulisine and stopped 30 minutes prior to dosing. The target blood glucose level for the last 30 minutes prior to trial product administration was 5.5 mmol/L (100 mg/dL) $\pm 10\%$ (upper and lower limits included). Once target blood glucose level was attained, the

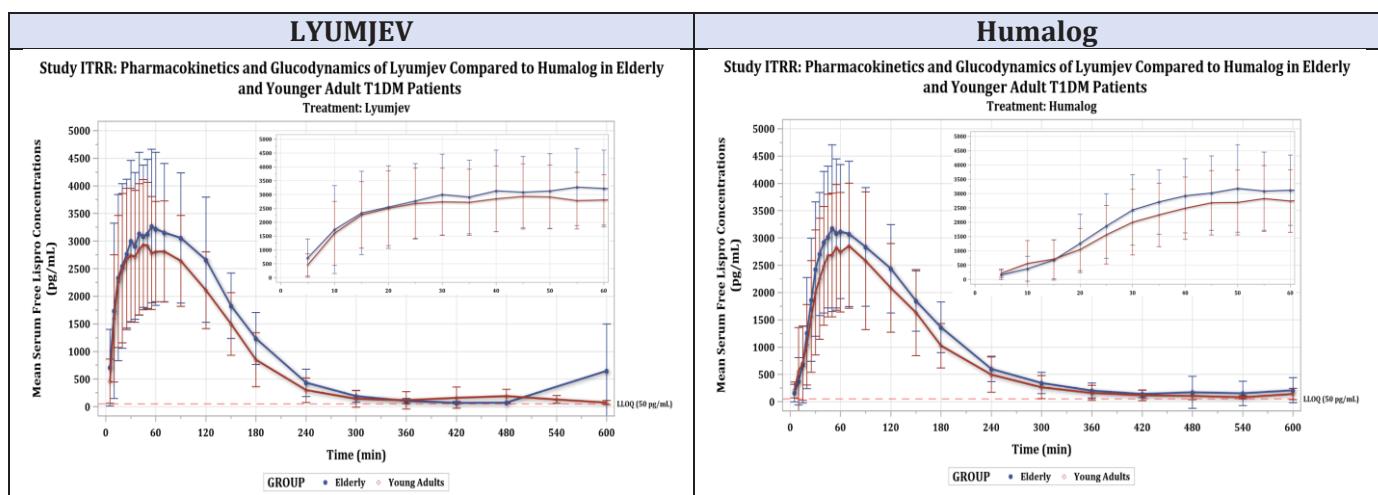
insulin product was administered, and the onset of action was defined as when blood glucose drops by 0.3 mmol/L (5 mg/dL) from baseline. Baseline was established as the mean of blood glucose concentrations at -6, -4, and -2 minutes prior to insulin product administration. Following onset of action, glucose infusion rate (GIR) was calculated using the automated glucose clamp. The automated glucose clamp allowed for continuous blood glucose monitoring and consequential glucose infusion to maintain a target blood glucose concentration of 5.5 mmol/L (100 mg/dL). Thus, blood glucose concentrations were kept constant while the GIR varied which reflected the GD activity of insulin. The clamp procedure continued for up to 10 hours after dose or until after blood glucose concentrations increased to >200 mg/dL (11.1 mmol/L) without any glucose being administered for at least 30 minutes, whichever was earlier.

Glucodynamic analyses were conducted on those subjects who completed at least 1 clamp procedure.

Serial blood samples were taken for the PK measurement of insulin lispro.

The mean insulin lispro exposure following administration of single doses of 15 U LYUMJEV and insulin lispro (Humalog) is presented in [Figure 9](#).

Figure 9 Mean (\pm SD) insulin lispro concentration versus time for the duration of the clamp (inset - for the first hour) by treatment following 15 U doses of LYUMJEV and Humalog in Elderly and Young Adult T1DM Patients



(Source: Reviewer generated graph)

Pharmacokinetics in Young Adult T1DM Patients:

Following doses of 15 U LYUMJEV or HUMALOG, a faster 5.6-minute earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-15min)}$, $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ ([Figure 9, Table 7](#)). Early 50% T_{max} for insulin lispro was reduced by approximately 49% following LYUMJEV administration compared to Humalog ([Table 7](#)). There were corresponding increases in $AUC_{(0-15min)}$, $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 7.2-fold, 2.7-fold, and 1.4-fold, respectively. However, the overall insulin exposure $AUC_{(0-\infty)}$, T_{max} , and C_{max} were not significantly different between LYUMJEV and Humalog. ([Table 7](#)).

Compared to Humalog, late insulin lispro exposure was reduced with LYUMJEV by 22% as measured by $AUC_{(2-10h)}$, and a 41% reduction in $AUC_{(3-10h)}$ ([Table 7](#)). The duration of insulin lispro in the serum was reduced by 74 minutes following LYUMJEV administration compared to Humalog. ([Table 7](#)).

Table 7 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in Young Adult T1DM Patients

Parameter	Treatment	N	Geometric LS Means	Ratio of Geometric LS Means (LY vs HL)	95% CI for the ratio (Lower, Upper)	P-value
C _{max} (pmol/L)	Humalog	39	543	1.06	(0.967, 1.16)	0.2138
	LY900014	40	574			
AUC(0-∞) (pmol·h/L)	Humalog	39	1181	1.03	(0.973, 1.09)	0.3087
	LY900014	40	1215			
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Parameter	Treatment	LS mean (N)	(LY900014 - Humalog)	Difference in LS means 95% CI for the difference (Lower, Upper)	P-value	Ratio of LS means 95% CI for the ratio (LY900014 : Humalog) (Lower, Upper)
t _{max} (h)	Humalog LY900014	1.03 (39) 0.946 (40)	-0.0818	(-0.298, 0.135)	0.4493	0.920 (0.737, 1.13)
Onset of Appearance (min)	Humalog LY900014	6.84 (38) 1.26 (40)	-5.58	(-7.18, -3.97)	<.0001	0.185 (0.122, 0.258)
Early 50% t _{max} (min)	Humalog LY900014	29.0 (38) 14.8 (39)	-14.2	(-17.5, -10.9)	<.0001	0.510 (0.416, 0.610)
Late 50% t _{max} (min)	Humalog LY900014	145 (37) 142 (40)	-2.32	(-17.8, 13.1)	0.7627	0.984 (0.883, 1.09)
Duration (min)	Humalog LY900014	445 (37) 371 (38)	-74.0	(-95.1, -52.9)	<.0001	0.833 (0.796, 0.873)

Abbreviations: CI = Confidence interval; Duration = Time from study drug administration until the serum insulin lispro concentrations reached the lower limit of quantification; Early 50% t_{max} = Time to early half-maximal drug concentration; Late 50% t_{max} = Time to late half-maximal drug concentration; LS = Least squares; N = Number of patients; Onset of Appearance = Time from study drug administration until the first time serum insulin lispro concentrations reached the lower limit of quantification; t_{max} = Time of maximum observed drug concentration
Model: PE = Period + Treatment + Sequence + Patient(Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect
The CIs for the ratio were calculated using the Fieller's theorem
P-value is for the test of the mean difference.

(Source: CSR for Study ITRR, Tables ITRR.7.2- ITRR.7.3 pp 33-34)

Pharmacokinetics in Elderly T1DM Patients:

Following doses of 15 U LYUMJEV or HUMALOG, a faster 5.5-minute earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max}, AUC_(0-15min), AUC_(0-30min), and AUC_(0-1h) (Figure 9, Table 8). Early 50% T_{max} for insulin lispro was reduced by approximately 44% following LYUMJEV administration compared to Humalog (Table 8). There were corresponding increases in AUC_(0-15min), AUC_(0-30min) and AUC_(0-1h) by approximately 7.2-fold, 2.4-fold, and 1.4-fold, respectively. However, the overall insulin exposure AUC_(0-∞), T_{max}, and C_{max} were not significantly different between LYUMJEV and Humalog. (Table 8).

Compared to Humalog, late insulin lispro exposure was reduced with LYUMJEV by 19% as measured by AUC_(2-10h), and a 39% reduction in AUC_(3-10h) (Table 8). The duration of insulin lispro in the serum was reduced by 72 minutes following LYUMJEV administration compared to Humalog. (Table 8).

Table 8 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in Elderly T1DM Patients

Parameter	Treatment	N	Geometric LS Means	Ratio of Geometric LS Means (LY vs HL)	95% CI for the ratio (Lower, Upper)	P-value			
C_{max} (pmol/L)	Humalog	37	574	1.07	(0.953, 1.20)	0.2449			
	LY900014	37	615						
$AUC(0-\infty)$ (pmol·h/L)	Humalog	37	1398	1.02	(0.947, 1.09)	0.6182			
	LY900014	37	1423						
Difference in LS means (LY900014 - Humalog)									
95% CI for the difference (Lower, Upper)									
Parameter Treatment LS mean (N) (LY900014 - Humalog)									
t _{max} (h)	Humalog	1.05 (37)							
	LY900014	1.08 (37)	0.0323	(-0.167, 0.232)	0.7443	1.03			
Onset of Appearance (min)	Humalog	6.85 (37)							
	LY900014	1.32 (37)	-5.53	(-7.46, -3.61)	<.0001	0.192			
Early 50% t _{max} (min)	Humalog	27.9 (37)							
	LY900014	15.6 (36)	-12.3	(-15.6, -8.94)	<.0001	0.560			
Late 50% t _{max} (min)	Humalog	156 (37)							
	LY900014	154 (37)	-1.68	(-16.5, 13.1)	0.8189	0.989			
Duration (min)	Humalog	475 (33)							
	LY900014	404 (37)	-71.7	(-95.1, -48.3)	<.0001	0.849			

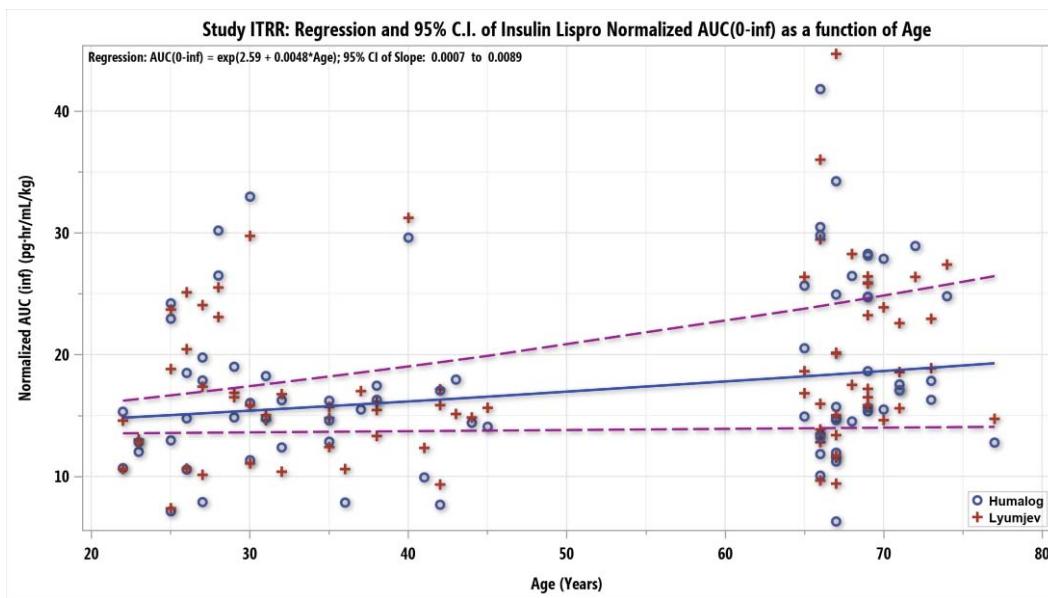
Abbreviations: CI = Confidence interval; Duration = Time from study drug administration until the serum insulin lispro concentrations reached the lower limit of quantification; Early 50% t_{max} = Time to early half-maximal drug concentration; Late 50% t_{max} = Time to late half-maximal drug concentration; LS = Least squares; N = Number of patients; Onset of Appearance = Time from study drug administration until the first time serum insulin lispro concentrations reached the lower limit of quantification; t_{max} = Time of maximum observed drug concentration
Model: PK = Period + Treatment + Sequence + Patient(Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect
The CIs for the ratio were calculated using the Fieller's theorem
P-value is for the test of the mean difference.

(Source: CSR for Study ITRR, Tables ITRR.7.4- ITRR.7.5 pp 35-36)

Age Interaction on PK Parameters

Age group-by-treatment interactions for $AUC(0-\infty)$ had a slope of 0.0048, indicating that the treatment effect between LYUMJEV and Humalog was similar for the age groups (Figure 10).

Figure 10 Regression and 95% C.I. of Insulin Normalized Lispro AUC_(0-inf) as a Function of Age in Elderly and Young Adult T1DM Patients

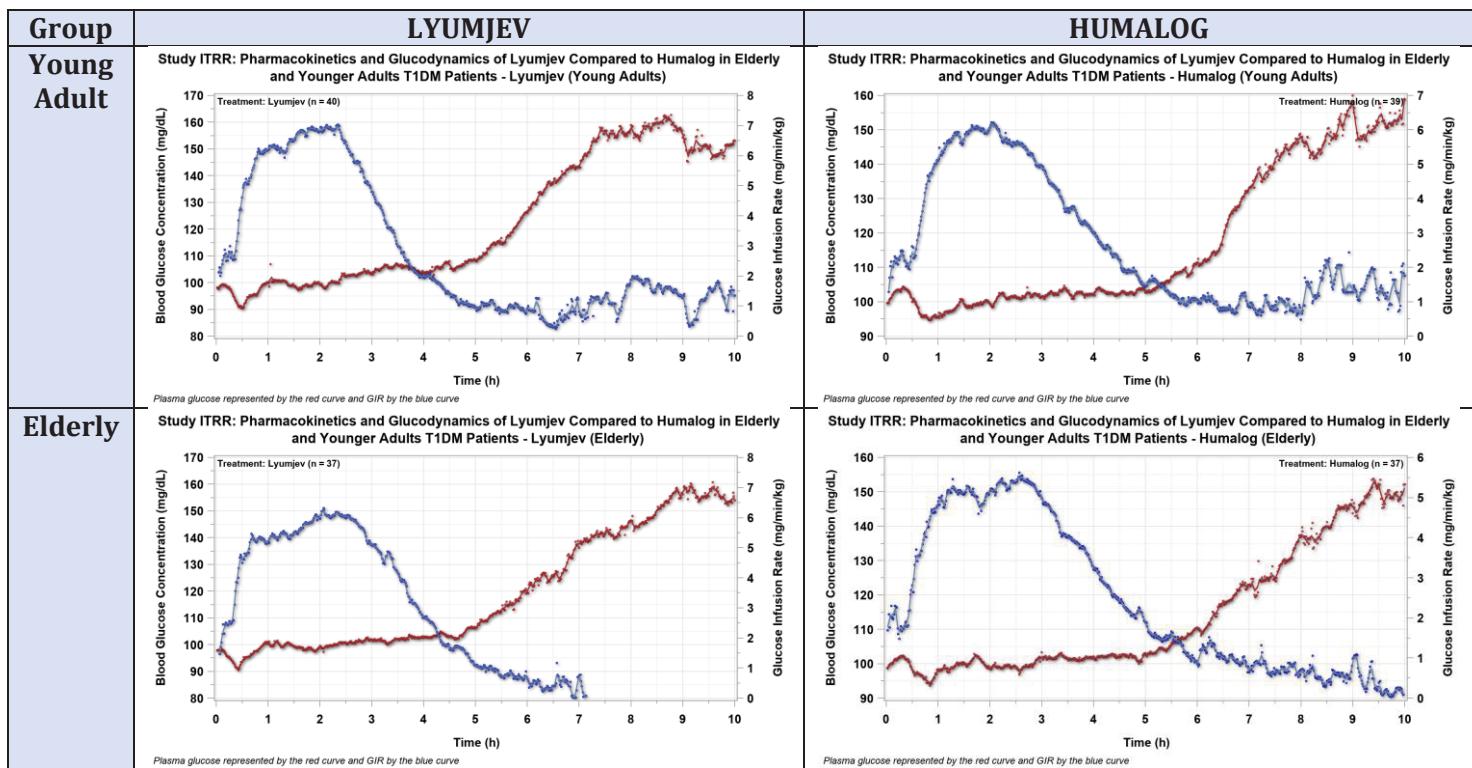


(Source: Reviewer generated graph)

Pharmacodynamics:

Mean blood glucose concentrations and GIR versus time and mean LOESS fits comparing a 15 U dose of LYUMJEV to 15 U Humalog in elderly and young adult T1DM patients are presented in [Figure 11](#).

Figure 11 Individual and Mean Blood Glucose Concentration and Glucose infusion Rate Following 15 U Doses of LYUMJEV or Humalog in Elderly and Young Adult T1DM Patients



(Source: Reviewer generated graph)

Glucodynamics in Young Adult T1DM Patients:

A slightly greater insulin onset of action and shorter duration was observed following LYUMJEV administration compared to Humalog ([Figure 11](#)). The onset of the insulin action (T_{onset}) was reduced by 11-minutes (reduction of 35%) for LYUMJEV compared to Humalog. There were corresponding 2.79-fold, 1.87-fold and 1.32-fold increases in the total amount of glucose infused $G_{tot(0-30min)}$, $G_{tot(0-1h)}$ and $G_{tot(0-2h)}$, respectively, following LYUMJEV compared to Humalog ([Table 9](#)).

There was a 29.52-minute difference in the late 50% tR_{max} reduction following administration of LYUMJEV compared to Humalog across the dose range. Compared to Humalog, following LYUMJEV administration glucose infused from 2, 3 and 4 hours to the end of the clamp, $G_{tot(2h-End)}$, $G_{tot(3h-End)}$ and $G_{tot(4h-End)}$ were reduced by 16%, 36%, and 54%, respectively. There was a shorter duration of action of 43.6 minutes following LYUMJEV compared to Humalog. Though R_{max} was significantly higher following LYUMJEV compared to Humalog, total glucose infused over the clamp duration (G_{tot}) and tR_{max} were similar between the treatments ([Table 9](#)).

Table 9 Pharmacodynamic Parameters and Statistical Analysis of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in Young Adult T1DM Patients

Parameter	Treatment	N	LS Means	Ratio of LS Means (LY vs HL)	95% CI for the Ratio (Lower, Upper)	p-value ^d	Difference in LS Means (LY – HL)	95% CI for the difference (Lower, Upper)	p-Value ^c	
R _{max} (mg/kg/min)	Humalog	39	6.23 ^b	1.14 ^b	(1.05, 1.25) ^b	0.0038 ^d	-	-	-	
	LY900014	40	7.13 ^b							
G _{tot} (mg/kg)	Humalog	39	1141.89 ^b	1.02 ^b	(0.94, 1.10) ^b	0.6248 ^d	-	-	-	
	LY900014	40	1164.29 ^b							
<hr/>										
Parameter	Treatment	LS mean (N)	Difference in LS means (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)	P-value	Ratio of LS means (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)			
tRmax (min)	Humalog	121.28 (39)								
	LY900014	115.04 (40)	-6.24	(-18.92, 6.43)	0.3249	0.95	(0.86, 1.05)			
Duration of Action (min)	Humalog	341.76 (39)								
	LY900014	298.19 (40)	-43.57	(-65.48, -21.66)	0.0003	0.87	(0.82, 0.93)			
Early 50% tRmax (min)	Humalog	47.25 (39)								
	LY900014	33.19 (40)	-14.06	(-18.54, -9.57)	<.0001	0.70	(0.63, 0.78)			
Late 50% tRmax (min)	Humalog	235.03 (39)								
	LY900014	205.52 (40)	-29.52	(-42.09, -16.94)	<.0001	0.87	(0.83, 0.92)			
Tonset (min)	Humalog	30.97 (39)								
	LY900014	20.13 (40)	-10.84	(-16.79, -4.89)	0.0007	0.65	(0.53, 0.81)			

Abbreviations: CI = Confidence interval; Early 50% tRmax = Time prior to tRmax when glucose infusion rate is half the maximum glucose infusion rate; Late 50% tRmax = Time after tRmax when glucose infusion rate is half the maximum glucose infusion rate; LS = Least squares;

N = Number of patients; Tonset = Time of first positive glucose infusion rate; tRmax = Time of the maximum glucose infusion rate
Model: GD = Period + Treatment + Sequence + Patient(Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect
The CIs for the ratio were calculated using the Fieller's theorem

P-value is for the test of the mean difference.

(Source: CSR for Study ITRR, Tables ITRR.7.11- ITRR.7.12 pp 47-48)

Glucodynamics in Elderly T1DM Patients:

A slightly greater insulin onset of action and shorter duration was observed following LYUMJEV administration compared to Humalog (Figure 11). The onset of the insulin action (T_{onset}) was reduced by 12-minutes (reduction of 38%) for LYUMJEV compared to Humalog. There were corresponding 3.16-fold, 1.69-fold and 1.31-fold increases in total amount of glucose infused G_{tot(0-30min)}, G_{tot(0-1h)} and G_{tot(0-2h)}, respectively, following LYUMJEV compared to Humalog (Table 10).

There was a 35-minute difference in the late 50% tR_{max} reduction following administration of LYUMJEV compared to Humalog across the dose range. Compared to Humalog, following LYUMJEV administration glucose infused from 3 and 4 hours to the end of the clamp, G_{tot(3h-End)} and G_{tot(4h-End)} were reduced by 22%, and 44%, respectively. There was a shorter duration of action of 34 minutes following LYUMJEV compared to Humalog. Though R_{max} was significantly higher and tR_{max} was significantly earlier following LYUMJEV compared to Humalog, total glucose infused over the clamp duration (G_{tot}) was similar between the treatments (Table 10).

Table 10 Pharmacodynamic Parameters and Statistical Analysis of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in Elderly T1DM Patients

Parameter	Treatment	N	LS Means	Ratio of LS Means (LY vs HL)	95% CI for the Ratio (Lower, Upper)	p-value ^d	Difference in LS Means (LY - HL)	95% CI for the difference (Lower, Upper)	p-value ^c
R _{max} (mg/kg/min)	Humalog	35	5.49 ^b	1.14 ^b	(1.03, 1.26)	0.0123 ^d	-		
	LY900014	37	6.26 ^b						
G _{tot} (mg/kg)	Humalog	35	1103.16 ^b	1.04 ^b	(0.96, 1.12)	0.3517 ^d	-		
	LY900014	37	1142.66 ^b						
<hr/>									
Parameter	Treatment	LS mean (N)	Difference in LS means (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)	P-value	Ratio of LS means (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)		
tRmax (min)	Humalog	150.13 (35)	-26.08	(-45.58, -6.58)	0.0102	0.83	(0.72, 0.95)		
	LY900014	124.05 (37)							
Duration of Action (min)	Humalog	352.01 (35)	-34.46	(-56.94, -11.98)	0.0037	0.90	(0.85, 0.96)		
	LY900014	317.55 (37)							
Early 50% tRmax (min)	Humalog	46.77 (35)	-9.93	(-17.53, -2.34)	0.0119	0.79	(0.64, 0.94)		
	LY900014	36.84 (37)							
Late 50% tRmax (min)	Humalog	263.03 (35)	-35.16	(-51.03, -19.28)	<.0001	0.87	(0.82, 0.92)		
	LY900014	227.88 (37)							
Tonset (min)	Humalog	30.78 (35)	-11.80	(-17.49, -6.11)	<.0001	0.62	(0.49, 0.78)		
	LY900014	18.98 (37)							

Abbreviations: CI = Confidence interval; Early 50% tRmax = Time prior to tRmax when glucose infusion rate is half the maximum glucose infusion rate; Late 50% tRmax = Time after tRmax when glucose infusion rate is half the maximum glucose infusion rate; LS = Least squares;

N = Number of patients; Tonset = Time of first positive glucose infusion rate; tRmax = Time of the maximum glucose infusion rate Model: GD = Period + Treatment + Sequence + Patient(Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect The CIs for the ratio were calculated using the Fieller's theorem

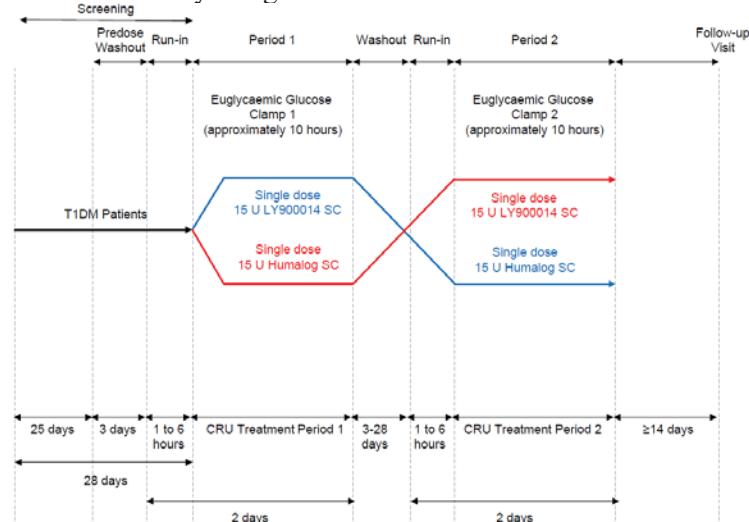
P-value is for the test of the mean difference.

(Source: CSR for Study ITRR, Tables ITRR.7.13-ITRR.7.14 pp 49-51)

Study ITRZ: PK/PD of LYUMJEV versus Humalog in Japanese patients with T1DM

Study ITRZ was a Phase 1, single center, randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study that compared the glucodynamics during a euglycemic clamp following administration of a single 15-U SC dose of LYUMJEV or Humalog in Japanese patients with T1DM.

A total of 31 Japanese patients with T1DM, 13 males and 18 females, between the ages of 18 and 56 years (mean=39.5 years), participated in this study. The mean body weight was 59.6 kg and the mean BMI was 22.85 kg/m². A schematic of the study design is shown below:



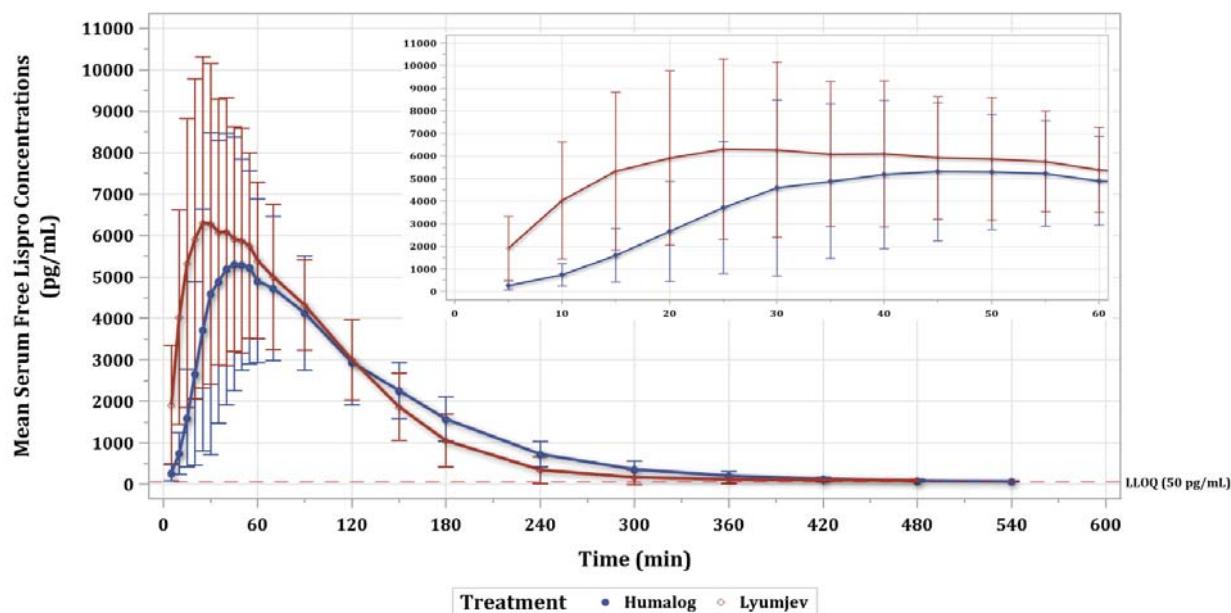
Glucodynamic assessments were determined from the glucose clamp procedure, in which the glucose infusion rate (GIR) over time was used as a measure of insulin effect. Glucodynamic analyses were conducted on those subjects who completed at least 1 clamp procedure.

Serial blood samples were taken for the PK measurement of insulin lispro.

The mean insulin lispro exposure following administration of single doses of 15 U LYUMJEV and insulin lispro (Humalog) is presented in [Figure 12](#).

Figure 12 Mean (\pm SD) insulin lispro concentration versus time for the duration of the clamp (inset - for the first hour) by treatment following 15 U doses of LYUMJEV and Humalog in Japanese T1DM Patients

Study ITRZ: Pharmacokinetics and Glucodynamics of Lyumjev Compared to Humalog in Japanese T1DM Patients



(Source: Reviewer generated graph)

Pharmacokinetics:

Following doses of 15 U LYUMJEV or HUMALOG, a faster 13-minute earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-15min)}$, $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ ([Figure 12, Table 11](#)). Early 50% T_{max} for insulin lispro was reduced by approximately 50% following LYUMJEV administration compared to Humalog. There were corresponding increases in $AUC_{(0-15min)}$, $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 4.8-fold, 2.43-fold, and 1.46-fold, respectively. Overall insulin exposure $AUC_{(0-\infty)}$ was not significantly different between LYUMJEV and Humalog. Insulin lispro C_{max} following LYUMJEV was statistically higher by 1.17-fold compared to Humalog ([Table 11](#)).

Compared to Humalog, late insulin lispro exposure was reduced with LYUMJEV by 47.5% as measured by $AUC_{(2-10h)}$, and a 66.4% reduction in $AUC_{(3-10h)}$. The duration of insulin lispro in the serum was reduced by 88 minutes following LYUMJEV administration compared to Humalog. ([Table 11](#)).

Table 11 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in Japanese T1DM Patients

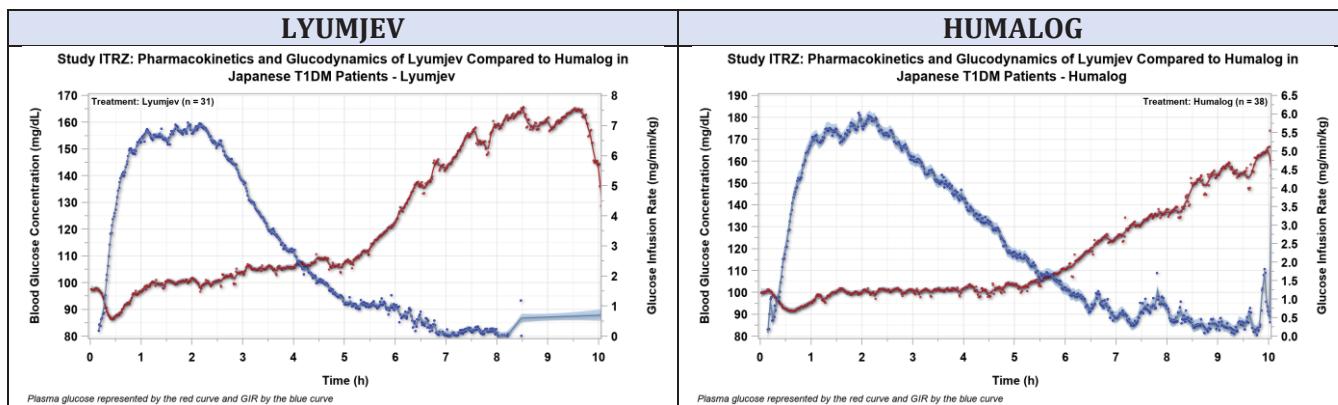
Parameter	Treatment	N	means	(LY900014 vs Humalog)	(Lower, Upper)	P-value
Cmax (pmol/L)	Humalog LY900014	30 31	930 1091	1.17	(1.00, 1.37)	0.0478
AUC(0-∞) (pmol.h/L)	Humalog LY900014	30 31	1990 1921	0.966	(0.802, 1.16)	0.7040

(Source: CSR for Study ITRZ, Table ITRZ.7.2 page 23)

Pharmacodynamics:

Mean blood glucose concentrations and GIR versus time and mean LOESS fits comparing a 15 U dose of LYUMJEV to 15 U Humalog in Japanese T1DM patients are presented in Figure 13.

Figure 13 Individual and Mean Blood Glucose Concentration and Glucose infusion Rate Following 15 U Doses of LYUMJEV or Humalog in Japanese T1DM Patients



(Source: Reviewer generated graph)

Glucodynamics:

A slightly greater insulin onset of action and shorter duration was observed following LYUMJEV administration compared to Humalog (Figure 13). The onset of the insulin action (T_{onset}) was reduced by 6.4-minutes (reduction of 27%) for LYUMJEV compared to Humalog. There were corresponding 2.16-fold, 1.57-fold and 1.28-fold increases in the total amount of glucose infused $G_{tot(0-30min)}$, $G_{tot(0-1h)}$ and $G_{tot(0-2h)}$, respectively, following LYUMJEV compared to Humalog (Table 12).

There was a 50.15-minute difference in the late 50% tR_{max} reduction following administration of LYUMJEV compared to Humalog. Compared to Humalog, following LYUMJEV administration glucose infused from 2, 3 and 4 hours to the end of the clamp, $G_{tot(2h-End)}$, $G_{tot(3h-End)}$ and $G_{tot(4h-End)}$ were reduced by 20%, 38%, and 58%, respectively. There was a shorter duration of action of 68.44 minutes following LYUMJEV compared to Humalog. Though R_{max} was significantly higher following LYUMJEV compared to Humalog, total glucose infused over the clamp duration (G_{tot}) was similar between the treatments (Table 12).

Table 12 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in Japanese T1DM Patients

Parameter	Treatment	N	Geometric least squares means	Ratio of geometric least squares means (LY900014 vs Humalog)	95% CI for the ratio (Lower, Upper)	P-value
Rmax (mg/kg/min)	Humalog	30	5.91			
	LY900014	30	6.73	1.14	(1.01, 1.28)	0.0337
Gtot (mg/kg)	Humalog	30	1265.71			
	LY900014	30	1168.38	0.92	(0.79, 1.08)	0.3173
Parameter	Treatment	LS mean (N)	Difference in LS means (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)	P-value	Ratio of LS means (LY900014 : Humalog)
tRmax (min)	Humalog	122.59 (30)				
	LY900014	102.86 (31)	-19.73	(-33.94, -5.52)	0.0082	0.84
Duration of Action (min)	Humalog	371.21 (30)				
	LY900014	302.77 (31)	-68.44	(-97.88, -39.01)	<.0001	0.82
Early 50% tRmax (min)	Humalog	40.45 (30)				
	LY900014	29.85 (31)	-10.60	(-13.98, -7.21)	<.0001	0.74
Late 50% tRmax (min)	Humalog	261.96 (30)				
	LY900014	211.81 (31)	-50.15	(-66.93, -33.38)	<.0001	0.81
Tonset (min)	Humalog	23.20 (30)				
	LY900014	16.83 (31)	-6.37	(-9.71, -3.03)	0.0003	0.73
						(0.62, 0.86)

Abbreviations: CI = Confidence interval; Early 50% tRmax = Time prior to tRmax when glucose infusion rate is half the maximum glucose infusion rate; Late 50% tRmax = Time after tRmax when glucose infusion rate is half the maximum glucose infusion rate; LS = Least squares; N = Number of patients; Tonset = Time of first positive glucose infusion rate; tRmax = Time of the maximum glucose infusion rate.

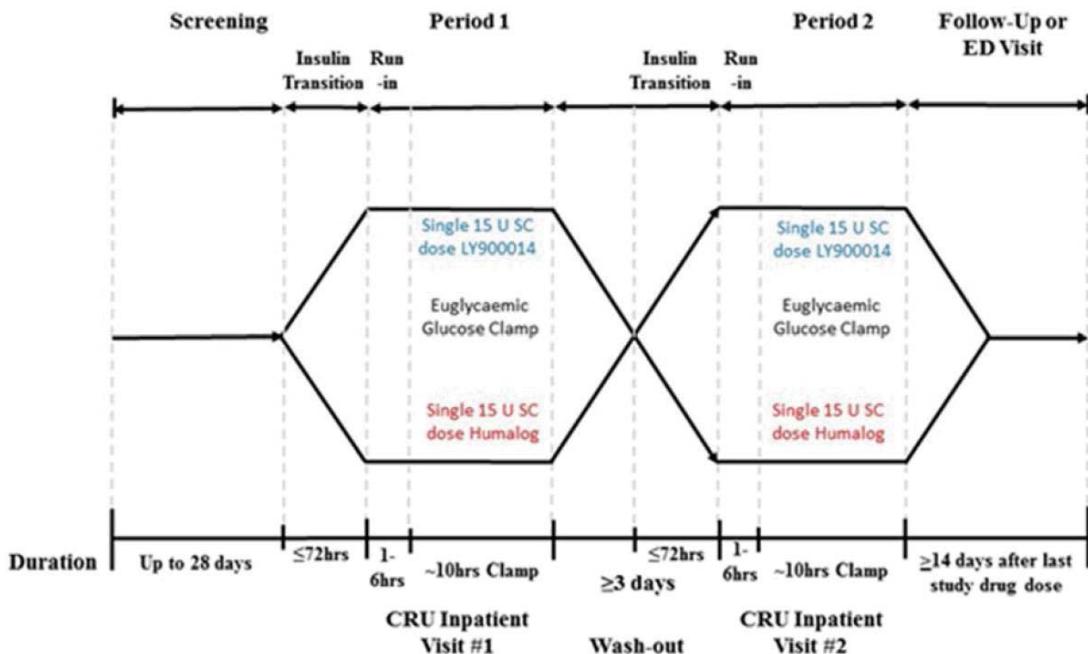
Model: GD = Period + Treatment + Sequence + Patient(Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect. The CIs for the ratio were calculated using the Fieller's theorem. P-value is for the test of the mean difference.

(Source: CSR for Study ITRZ, Tables ITRZ.7.7 - ITRZ.7.9 pp 34-36)

Study ITRU: PK/PD of LYUMJEV versus Humalog in patients with T2DM

Study ITRU was a Phase 1, randomized, patient- and investigator-blind, 2-treatment, single-dose, 2-period, 10-hour glycemic clamp, crossover study that compared the glucodynamics during a euglycemic clamp following administration of a single 15-U SC dose of LYUMJEV or Humalog in patients with T2DM.

A total of 38 patients, 35 male and 3 females, between the ages of 38 and 70 years (mean=60 years), participated in this study. The mean body weight was 93.3 kg and the mean BMI was 30.02 kg/m². A schematic of the study design is shown below:



Abbreviations: CRU = clinical research unit; SC = subcutaneous.

An automated glucose clamp (ClampArt) was used in the study to maintain a target glucose level through infusion of a 20% D-glucose (dextrose) solution after the administration of a dose of insulin. A 1 to 6-hour run-in period was conducted to stabilize the patient's blood glucose level through the use of a variable infusion of either glucose or insulin (insulin glulisine) and stopped 30 minutes prior to dosing. The target blood glucose level for the last 30 minutes prior to trial product administration was 5.5 mmol/L (100 mg/dL) \pm 10% (upper and lower limits included). Once target blood glucose level was attained, the insulin product was administered (time=0), and the onset of action was defined as when blood glucose dropped by 0.3 mmol/L (5 mg/dL) from baseline. Baseline was established as the mean of blood glucose concentrations at -6, -4, and -2 minutes prior to study drug administration. Following onset of action, glucose infusion rate (GIR) was calculated using the automated glucose clamp. The automated glucose clamp allowed for continuous blood glucose monitoring and consequential glucose infusion to maintain a target blood glucose concentration of 5.5 mmol/L (100 mg/dL). Thus, blood glucose concentrations were kept constant while the GIR varied reflecting the glucodynamic (GD) activity of insulin.

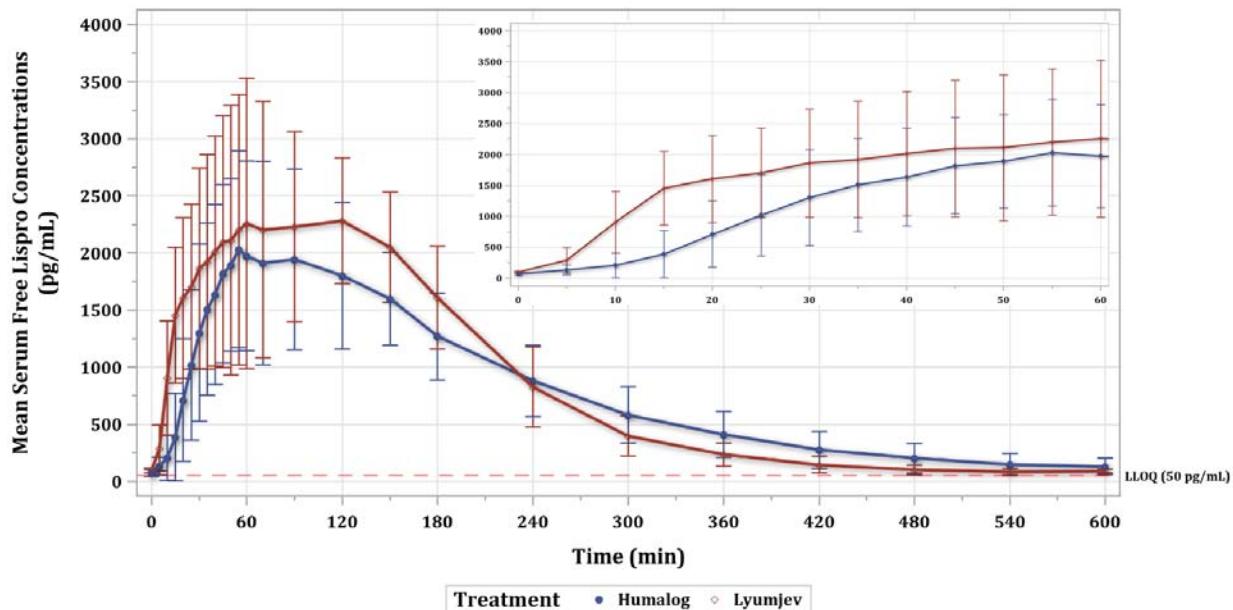
Glucodynamic analyses were conducted on those subjects who completed at least 1 clamp procedure.

Serial blood samples were taken for the PK measurement of insulin lispro.

The mean insulin lispro exposure following administration of single doses of 15 U LYUMJEV and insulin lispro (Humalog) is presented in [Figure 14](#).

Figure 14 Mean (\pm SD) insulin lispro concentration versus time for the duration of the clamp (inset - for the first hour) by treatment following 15 U doses of LYUMJEV and Humalog in T2DM Patients

Study ITRU: Pharmacokinetics and Glucodynamics of Lyumjev Compared to Humalog in T2DM Patients



(Source: Reviewer generated graph)

Pharmacokinetics:

Following doses of 15 U LYUMJEV or HUMALOG, a faster 5.31-minute earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-15min)}$, $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ (Figure 14, Table 13). Early 50% T_{max} for insulin lispro was reduced by approximately 37% following LYUMJEV administration compared to Humalog. There were corresponding increases in $AUC_{(0-15min)}$, $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 46.38-fold, 2.92-fold, and 1.46-fold, respectively. Overall insulin exposure $AUC_{(0-\infty)}$ or T_{max} were not significantly different between LYUMJEV and Humalog. There was an increase in insulin lispro C_{max} following LYUMJEV compared to Humalog (Table 13).

Compared to Humalog, late insulin lispro exposure was reduced with LYUMJEV by 26% as measured by $AUC_{(3-10h)}$, and a 66.4% reduction in $AUC_{(3-10h)}$. The duration of insulin lispro in the serum was reduced by 50.8 minutes following LYUMJEV administration compared to Humalog (Table 13).

Table 13 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in T2DM Patients

Parameter	Treatment	N	Geometric least squares means	Ratio of geometric least squares means (LY900014 vs Humalog)	95% CI for the ratio (Lower, Upper)	P-value
Cmax (pmol/L)	15 U Humalog SC 15 U LY900014 SC	38 38	370 441	1.19	(1.09, 1.31)	0.0005
AUC(0-∞) (pmol.h/L)	15 U Humalog SC 15 U LY900014 SC	38 38	1321 1387	1.05	(0.996, 1.11)	0.0676
tmax (h)	Humalog LY900014	1.42 (38) 1.63 (38)	0.211	(-0.109, 0.530)	0.1891	1.15 (0.930, 1.42)
Onset of Appearance (min)	Humalog LY900014	7.28 (33) 1.97 (33)	-5.31	(-6.65, -3.98)	<0.0001	0.271 (0.145, 0.374)
Early 50% tmax (min)	Humalog LY900014	29.6 (38) 18.6 (38)	-10.9	(-15.2, -6.63)	<0.0001	0.630 (0.518, 0.758)
Late 50% tmax (min)	Humalog LY900014	223 (38) 209 (38)	-14.3	(-36.4, 7.78)	0.1974	0.936 (0.851, 1.04)
Duration (min)	Humalog LY900014	559 (18) 508 (31)	-50.8	(-93.5, -8.05)	0.0220	0.909 (0.854, 0.965)

Abbreviations: AUC(0-∞) = Area under the concentration versus time curve from time zero to infinity; AUC(0-15min) = Area under the concentration versus time curve from time zero to 15 minutes postdose; AUC(0-30min) = Area under the concentration versus time curve from time zero to 30 minutes postdose; AUC(0-1h) = Area under the concentration versus time curve from time zero to 1 hour postdose; AUC(2-10h) = Area under the concentration versus time curve from time 2 to 10 hours postdose; AUC(3-10h) = Area under the concentration versus time curve from time 3 to 10 hours postdose; CI = Confidence interval; Cmax = Maximum observed concentration; N = Number of patients

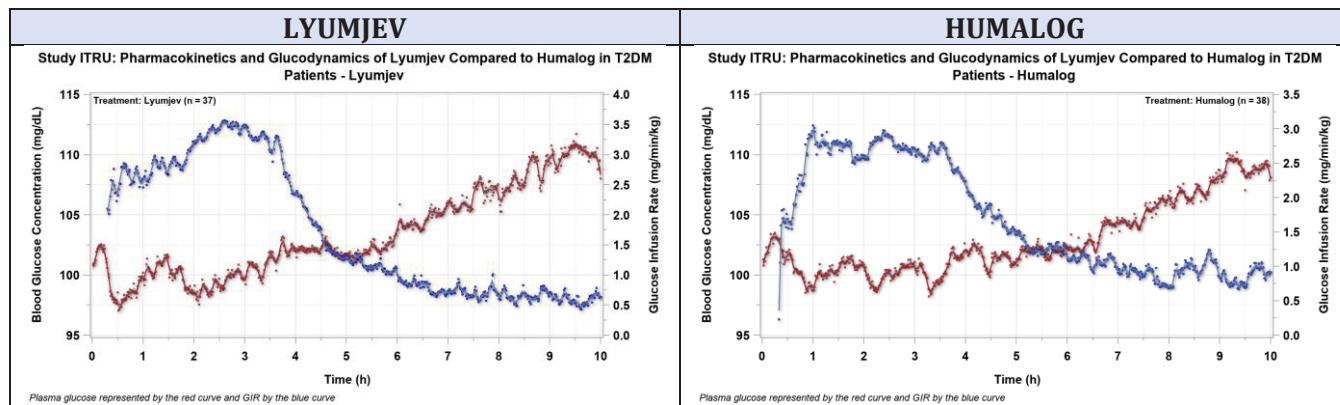
Abbreviations: CI = Confidence interval; Duration = Time from study drug administration until the serum insulin lispro concentrations reached the lower limit of quantification; Early 50% tmax = Time to early half-maximal drug concentration; Late 50% tmax = Time to late half-maximal drug concentration; LS = Least squares; N = Number of patients; Onset of Appearance = Time from study drug administration until the first time serum insulin lispro concentrations reached the lower limit of quantification; tmax = time of maximum observed drug concentration Model: PK = Period + Treatment + Sequence + Patient(Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect The CIs for the ratio were calculated using the Fieller's theorem P-value is for the test of the mean difference.

(Source: CSR for Study ITRU, Tables ITRU.7.2 and ITRU.7.3, pp 24-25)

Pharmacodynamics:

Individual blood glucose concentrations and GIR versus time and mean LOESS fits comparing a 15 U dose of LYUMJEV to 15 U Humalog in T2DM patients are presented in [Figure 15](#).

Figure 15 Individual and Mean Blood Glucose Concentration and Glucose infusion Rate Following 15 U Doses of LYUMJEV or Humalog in T2DM Patients



(Source: Reviewer generated graph)

Glucodynamics:

A slightly greater insulin onset of action and shorter duration was observed following LYUMJEV administration compared to Humalog (Figure 15). The onset of the insulin action (T_{onset}) was reduced by 12.7-minutes (reduction of 28%) for LYUMJEV compared to Humalog. There were corresponding 4.3-fold, 1.76-fold and 1.31-fold increases in the total amount of glucose infused $G_{tot(0-30min)}$, $G_{tot(0-1h)}$ and $G_{tot(0-2h)}$, respectively, following LYUMJEV compared to Humalog (Table 14).

There was a 19% reduction in the amount of glucose infused from 4 hours to the end of the clamp ($G_{tot[4h-End]}$) following LYUMJEV compared to Humalog. The shifts in the early and late insulin action resulted in a 27% higher R_{max} with LYUMJEV compared to Humalog. Following LYUMJEV, there was a significantly higher total glucose infused over the clamp duration (G_{tot}) compared to Humalog (Table 14).

Table 14 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog in T2DM Patients

Parameter	Treatment	N	Geometric Least Squares Means	Ratio of Geometric Least Squares Means (LY900014 versus Humalog)	95% CI for the Ratio (Lower, Upper)	p-value ^a	Difference in LS means (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)	p-Value ^b
R_{max} (mg/kg/min)	Humalog	38	2.83	1.27	(1.12, 1.45)	0.0006	-	-	-
	LY900014	37	3.61						
G_{tot} (mg/kg)	Humalog	38	652.75	1.12	(1.00, 1.26)	0.0488	-	-	-
	LY900014	37	734.08						
Difference in LS means (LY900014 - Humalog) 95% CI for the difference (Lower, Upper) Ratio of LS means (LY900014 : Humalog) 95% CI for the ratio (Lower, Upper)									
Parameter	Treatment	LS mean (N)	(LY900014 - Humalog)						
tR_{max} (min)	15 U Humalog SC 15 U LY900014 SC	145.77 (37) 159.42 (37)		13.64	(-8.37, 35.65)	0.2167	1.09	(0.95, 1.27)	
Duration of Action (min)	15 U Humalog SC 15 U LY900014 SC	401.96 (38) 384.87 (37)		-17.10	(-59.26, 25.07)	0.4162	0.96	(0.86, 1.07)	
Early 50% tR_{max} (min)	15 U Humalog SC 15 U LY900014 SC	55.75 (37) 54.01 (37)		-1.74	(-11.11, 7.62)	0.7077	0.97	(0.81, 1.14)	
Late 50% tR_{max} (min)	15 U Humalog SC 15 U LY900014 SC	265.09 (37) 245.65 (37)		-19.44	(-54.55, 15.68)	0.2686	0.93	(0.82, 1.06)	
T_{onset} (min)	15 U Humalog SC 15 U LY900014 SC	44.69 (38) 31.99 (37)		-12.70	(-18.44, -6.96)	<.0001	0.72	(0.62, 0.82)	

Abbreviations: CI = Confidence interval; Early 50% tR_{max} = Time prior to tR_{max} when glucose infusion rate is half the maximum glucose infusion rate; Late 50% tR_{max} = Time after tR_{max} when glucose infusion rate is half the maximum glucose infusion rate; LS = Least squares; N = Number of patients; T_{onset} = Time of first positive glucose infusion rate; tR_{max} = Time of the maximum glucose infusion rate

Model: GD = Period + Treatment + Sequence + Patient(Sequence) + Random Error, where Patient(Sequence) is fitted as a random effect The CIs for the ratio were calculated using the Fieller's theorem P-value is for the test of the mean difference.

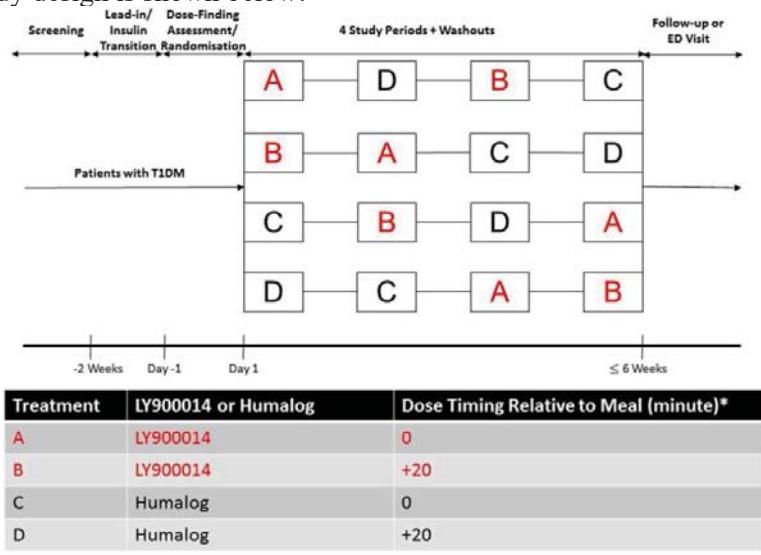
(Source: CSR for Study ITRU, Tables ITRU.7.6 and ITRU.7.7, pp 31-32)

Study ITRV: LYUMJEV versus Humalog immediately before and 20 minutes after a test meal (Mixed Meal Tolerance Test) in T1DM patients

Pharmacokinetics

Study ITRV was a randomized, patient- and investigator-blind, 2-treatment, 4-period crossover study in patients with T2DM to evaluate the PK of insulin lispro following a single SC injection of LYUMJEV and Humalog. The study also compared the effect of administering LYUMJEV or Humalog immediately before and 20 minutes after the start of the meal on the glucodynamic response.

A total of 36 patients, 27 male and 9 female, between the ages of 23 and 69 years (mean=45.4 years), participated in this study. The mean body weight was 80.6 kg and the mean BMI was 25.39 kg/m². A schematic of the study design is shown below:



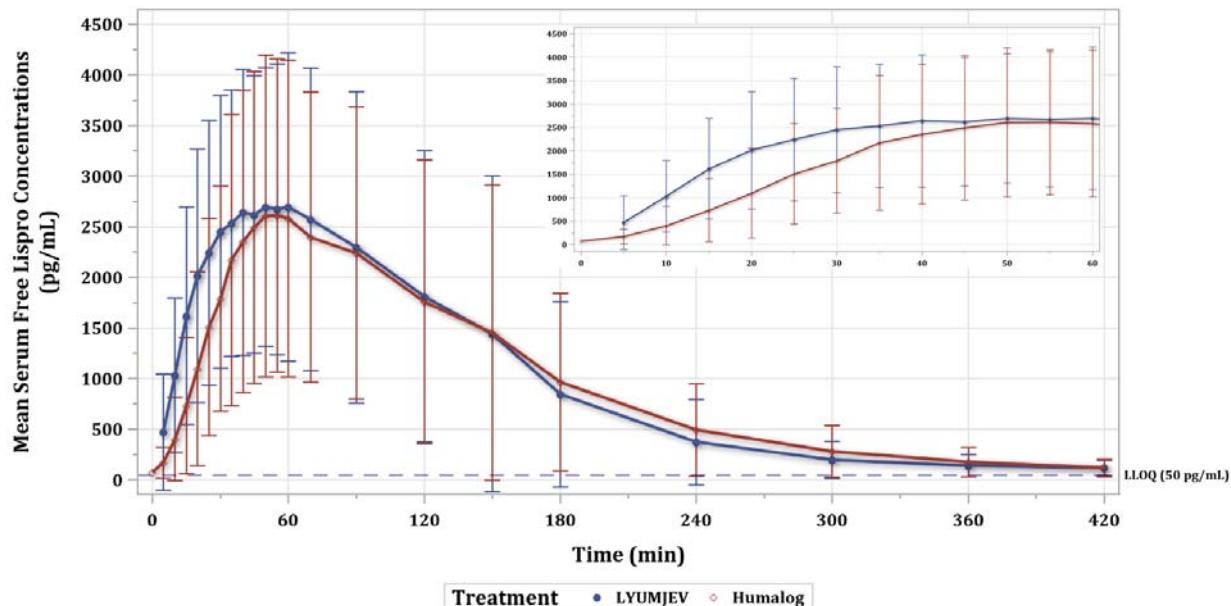
After the patients were admitted to the clinical research unit (CRU) in Period 1, a dose-finding assessment was conducted to determine an appropriate, individualized insulin lispro dose of LYUMJEV or Humalog to be administered with the standardized liquid test meal during the study MMTTs.

Serial blood samples were taken for the PK measurement of insulin lispro. During this mixed-meal tolerance test, the insulin lispro PK profiles following administrations of LYUMJEV and Humalog were assessed 2 times for each treatment over the 4 study periods. Since the PK of subcutaneously administered insulin lispro would not be affected by the timing of meal (immediately before or 20 minutes following the start of the meal), the PK of LYUMJEV and Humalog were calculated independently of the timing of the dose.

The mean insulin lispro exposure following administration of single doses of 15 U LYUMJEV and insulin lispro (Humalog) independent of the timing of dose in relation to a test meal is presented in [Figure 16](#).

Figure 16 Mean (\pm SD) insulin lispro concentration versus time (inset - for the first hour) by treatment following 15 U doses of LYUMJEV and Humalog independent of the timing of dose in relation to a test meal in T1DM Patients

Study ITRV: Pharmacokinetics and Glucodynamics of Lyumjev Compared to Humalog in T1DM Patients



(Source: Reviewer generated graph)

Following doses of 15 U LYUMJEV or HUMALOG, a faster 3.7-minute earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-15min)}$, $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ (Figure 16, Table 15). Early 50% T_{max} for insulin lispro was reduced by approximately 45.6% following LYUMJEV administration compared to Humalog. There were corresponding increases in $AUC_{(0-15min)}$, $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 4.49-fold, 2.37-fold, and 1.34-fold, respectively. Overall insulin exposure $AUC_{(0-\infty)}$ $AUC_{(0-tlast)}$, T_{max} , or C_{max} were not significantly different between LYUMJEV and Humalog (Table 15).

Compared to Humalog, late insulin lispro exposure was reduced with LYUMJEV by 28.1% as measured by $AUC_{(2-7h)}$, and a 44.3% reduction in $AUC_{(3-7h)}$. The duration of insulin lispro in the serum was reduced by 49 minutes following LYUMJEV administration compared to Humalog. (Table 15).

Table 15 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog independent of the timing of dose in relation to a test meal in T1DM Patients

Parameter	Treatment	n	N	Geometric least squares means	Ratio of geometric least squares means (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)	P-value
Cmax (pmol/L)	Humalog	69	35	452			
	LY900014	69	35	487	1.08	(0.999, 1.16)	0.0546
AUC(0-∞) (pmol.h/L)	Humalog	69	35	982			
	LY900014	69	35	962	0.980	(0.923, 1.04)	0.5048
Parameter	Treatment	LS mean (n)	[N]	Difference in LS means (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)	Ratio of LS means P-value (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)
t _{max} (h)	Humalog	0.949 (69)	[35]				
	LY900014	0.841 (69)	[35]	-0.107	(-0.217, 0.002)	0.0561	0.887 (0.793, 0.985)
Onset of Appearance (min)	Humalog	4.77 (68)	[35]				
	LY900014	1.07 (69)	[35]	-3.69	(-4.62, -2.76)	<.0001	0.225 (0.172, 0.296)
Early 50% t _{max} (min)	Humalog	26.1 (69)	[35]				
	LY900014	14.2 (67)	[35]	-11.9	(-13.6, -10.2)	<.0001	0.544 (0.479, 0.608)
Late 50% t _{max} (min)	Humalog	142 (68)	[35]				
	LY900014	132 (68)	[35]	-9.93	(-17.8, -2.04)	0.0141	0.930 (0.868, 0.995)
Duration (min)	Humalog	391 (33)	[20]				
	LY900014	342 (56)	[30]	-49.0	(-64.8, -33.1)	<.0001	0.875 (0.827, 0.923)

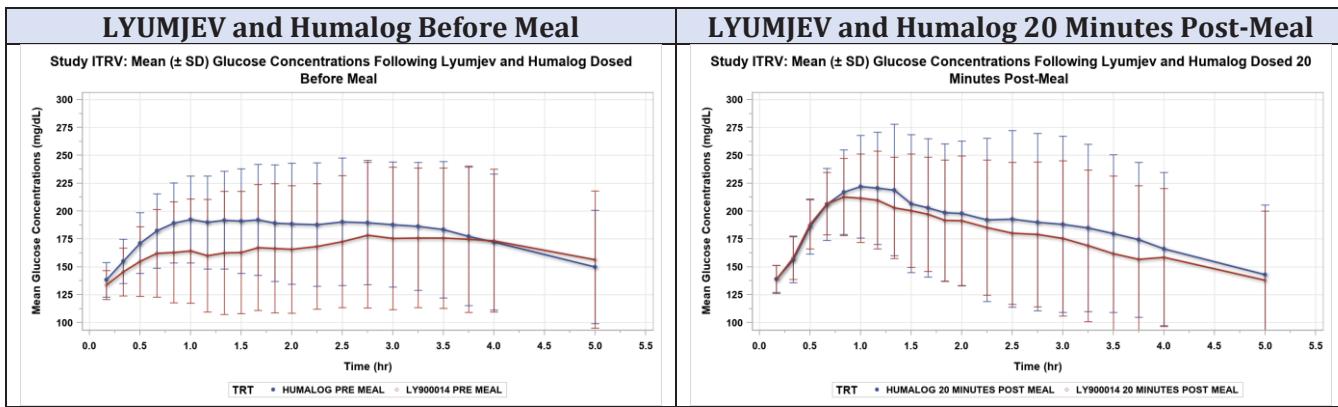
Abbreviations: CI = Confidence interval; Duration = Time from study drug administration until the serum insulin lispro concentrations reached the lower limit of quantification; Early 50% t_{max} = Time to early half-maximal drug concentration; Late 50% t_{max} = Time to late half-maximal drug concentration; LS = Least squares; N = Number of patients; n = Number of observations; Onset of Appearance = Time from study drug administration until the first time serum insulin lispro concentrations reached the lower limit of quantification; t_{max} = time of maximum observed drug concentration
Model: PK = Period + Treatment + Patient + Random Error, where Patient is fitted as a random effect
The CIs for the ratio were calculated using the Fieller's theorem. P-value is for the test of the mean difference.

(Source: CSR for Study ITRV, Tables ITRV.7.2 and ITRV.7.3, pp 30-32)

Pharmacodynamics:

Mean blood glucose concentrations following individualized insulin lispro dose of LYUMJEV or Humalog in T1DM patients are presented in [Figure 17](#).

Figure 17 Individual and Mean Blood Glucose Concentration Following Individualized Doses of LYUMJEV or Humalog Before Meals or 20 Minutes Post-Meal in T1DM Patients



(Source: Reviewer generated graph)

Following dosing LYUMJEV exhibited an earlier glucose-lowering effect compared to Humalog when dosed immediately before the start of the meal. When dosed 20 minutes following the start of the meal,

the trend toward a lower postprandial glucose excursion over the complete 5-hour MMTT were similar between LYUMJEV and Humalog (Figure 17).

LYUMJEV reduced the change from baseline in blood glucose by 27.30 mg/dL at 1 hour and by 21.89 mg/dL at 2 hours compared to Humalog (Table 16). LYUMJEV reduced change from baseline postprandial glucose excursions up to 4 hours post-meal ($BG\Delta AUC_{[0-30min]}$, $BG\Delta AUC_{[0-1h]}$, $BG\Delta AUC_{[0-2h]}$, $BG\Delta AUC_{[0-3h]}$, and $BG\Delta AUC_{[0-4h]}$) significantly compared to Humalog when the insulins were administered immediately before the start of the meal. Compared to Humalog, LYUMJEV reduced the change from baseline postprandial glucose excursions at 4 hours by 35%. LYUMJEV reduced the total postprandial glucose excursion during the 5-hour MMTT by 32% compared with Humalog, however, the difference in the was not statistically significant.

Following administration 20 minutes after the start of the meal, LYUMJEV reduced the postprandial glucose excursion during the 5-hour MMTT by 18%, however, the difference was not statistically significant.

An exploratory analysis comparing postprandial glucose when LYUMJEV was dosed 20 minutes following the start of the meal compared to Humalog dosed immediately before the start of the meal showed that the postprandial glucose excursion over the 5-hour MMTT was similar.

Table 16 Statistical Analysis of the Change from Baseline in Glucodynamic Endpoints Following the Mixed Meal Tolerance Test of LYUMJEV Compared to Humalog in T1DM Patients

Parameter	Treatment	LS mean (N)	Difference in LS means (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)	P-value	Ratio of LS means (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)
Glucose $\Delta AUC(0-5h)$ (mg.h/dL)	Humalog (0 min)	216.73 (32)	-14.50	(-94.38, 65.38)	0.7190	0.93	(0.65, 1.31)
	LY900014 (0 min)	202.23 (30)					
	Humalog (+20 min)	314.06 (29)					
	LY900014 (+20 min)	264.95 (29)					
$\Delta BGmax$ (mg/dL)	Humalog (0 min)	89.39 (35)	-10.27	(-27.06, 6.51)	0.2274	0.89	(0.70, 1.10)
	LY900014 (0 min)	79.11 (35)					
	Humalog (+20 min)	114.79 (35)					
	LY900014 (+20 min)	104.49 (35)					

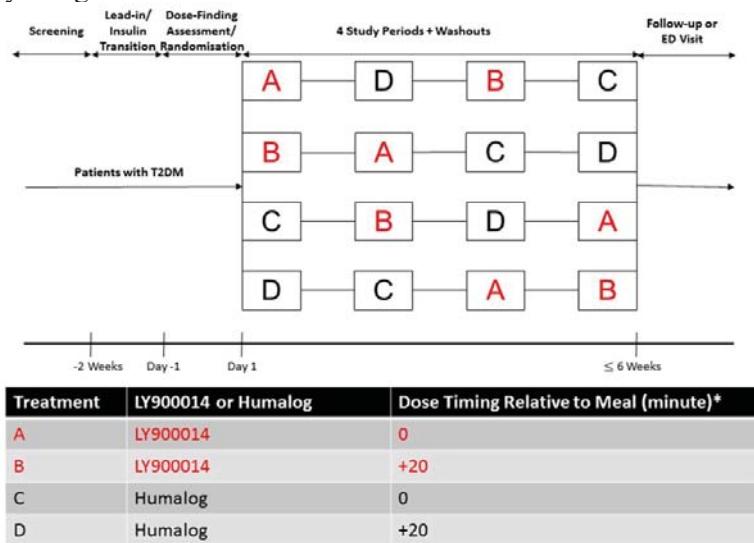
(Source: CSR for Study ITRV, Table ITRV.7.10, pp 45, 47)

Study ITRW: LYUMJEV versus Humalog immediately before and 20 minutes after a test meal (Mixed Meal Tolerance Test) in T2DM patients

Pharmacokinetics:

Study ITRW was a Phase 1, patient- and investigator-blind, randomized, 2-treatment, 4-period crossover study in patients with T2DM to evaluate the PK of insulin lispro following a single SC injection of LYUMJEV and Humalog. The study also compared the effect of administering LYUMJEV or Humalog immediately before and 20 minutes after the start of the meal on the glucodynamic response.

A total of 36 patients, 31 male and 5 female, between the ages of 48 and 70 years (mean=60.8 years), participated in this study. The mean body weight was 96.3 kg and the mean BMI was 30.91 kg/m². A schematic of the study design is shown below:



* Time 0 is immediately before test meal

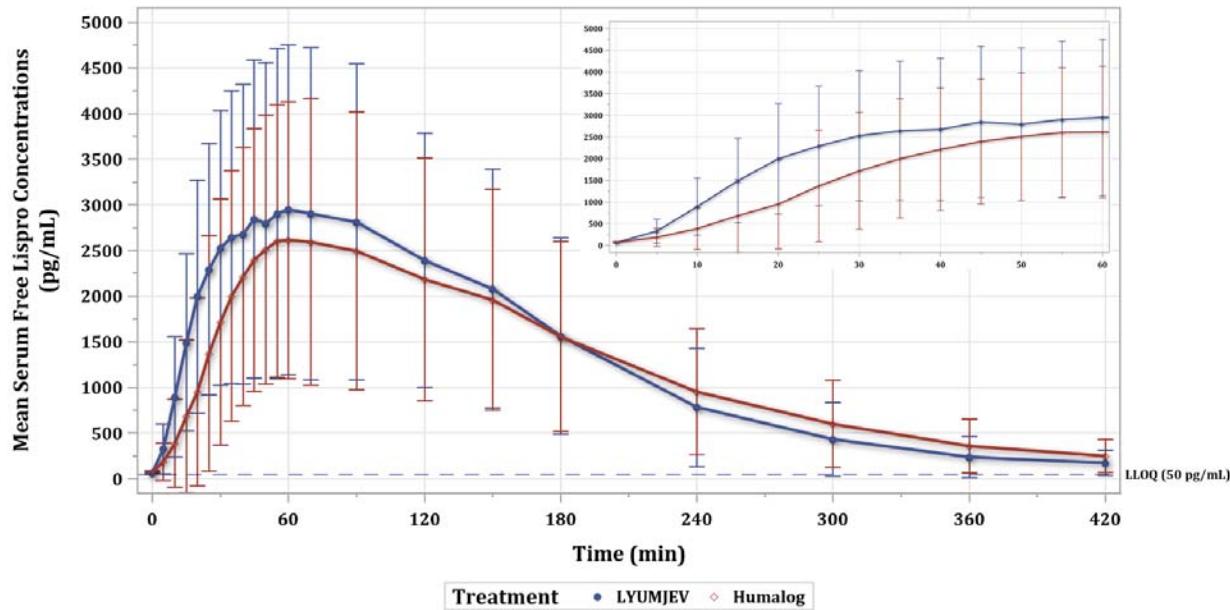
Abbreviations: ED = early discontinuation; T2DM = type 2 diabetes mellitus

Serial blood samples were taken for the PK measurement of insulin lispro. During this mixed-meal tolerance test, the insulin lispro PK profiles following administrations of LYUMJEV and Humalog were assessed 2 times for each treatment over the 4 study periods. Since the PK of subcutaneously administered insulin lispro would not be affected by the timing of meal (immediately before or 20 minutes following the start of the meal), the PK of LYUMJEV and Humalog were calculated independently of the timing of the dose.

The mean insulin lispro exposure following administration of single doses of 15 U LYUMJEV and insulin lispro (Humalog) independent of the timing of dose in relation to a test meal is presented in [Figure 18](#).

Figure 18 Mean (\pm SD) insulin lispro concentration versus time (inset - for the first hour) by treatment following 15 U doses of LYUMJEV and Humalog independent of the timing of dose in relation to a test meal in T1DM Patients

Study ITRW: Pharmacokinetics and Glucodynamics of Lyumjev Compared to Humalog in T2DM Patients



(Source: Reviewer generated graph)

Following doses of 15 U LYUMJEV or HUMALOG, a faster 5.5-minute earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-15min)}$, $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ (Figure 18, Table 17). Early 50% T_{max} for insulin lispro was reduced by approximately 47.3% following LYUMJEV administration compared to Humalog. There were corresponding increases in $AUC_{(0-15min)}$, $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 4.79-fold, 3.47-fold, and 1.65-fold, respectively. Overall insulin exposure $AUC_{(0-\infty)}$ and T_{max} , were not significantly different between LYUMJEV and Humalog. There was a 15% higher C_{max} following LYUMJEV compared to Humalog (Table 17).

Compared to Humalog, late insulin lispro exposure was reduced with LYUMJEV by 15.2% as measured by $AUC_{(2-7h)}$, and a 33.4% reduction in $AUC_{(3-7h)}$. The duration of insulin lispro in the serum was reduced by 18.7 minutes following LYUMJEV administration compared to Humalog. (Table 17).

Table 17 Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog independent of the timing of dose in relation to a test meal in T2DM Patients

Parameter	Treatment	n	N	Geometric least squares means	Ratio of geometric least squares means (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)	P-value	
Cmax (pmol/L)	Humalog	70	35	426				
	LY900014	70	35	489	1.15	(1.07, 1.23)	0.0002	
AUC(0-∞) (pmol.h/L)	Humalog	70	35	1307				
	LY900014	70	35	1337	1.02	(0.975, 1.07)	0.3503	
				Difference in LS means [N] (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)			
Parameter	Treatment	LS mean (n)	[N]	(LY900014 - Humalog)	P-value	Ratio of LS means (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)	
tmax (h)	Humalog	1.23 (70)	[35]	-0.105	(-0.273, 0.063)	0.2189	0.915	(0.769, 1.09)
Onset of Appearance (min)	Humalog	7.23 (62)	[33]	-5.52	(-6.90, -4.15)	<.0001	0.236	(0.179, 0.294)
Early 50% tmax (min)	Humalog	31.0 (70)	[35]	-14.7	(-16.8, -12.5)	<.0001	0.527	(0.463, 0.594)
Late 50% tmax (min)	Humalog	197 (69)	[35]	-18.7	(-29.9, -7.56)	0.0012	0.905	(0.856, 0.957)

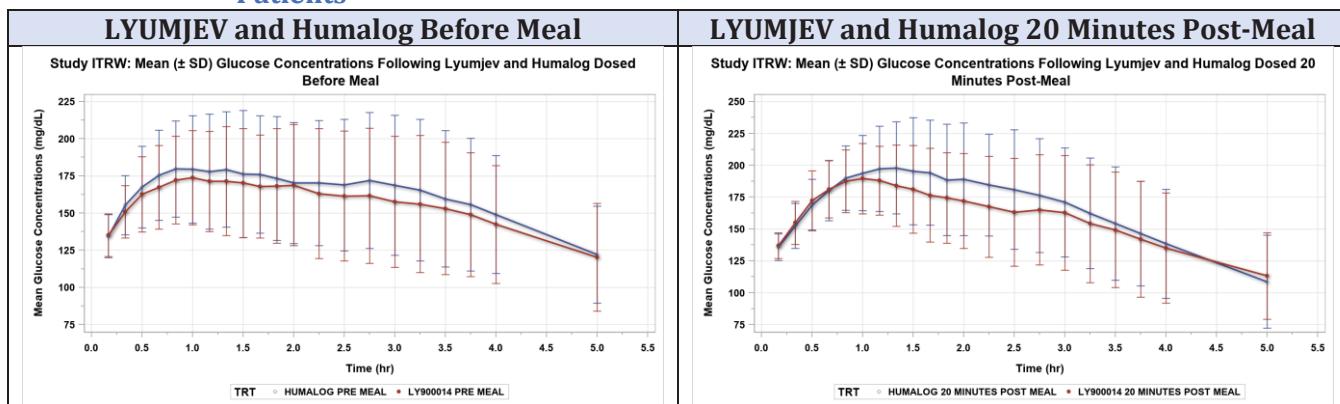
Abbreviations: CI = Confidence interval; Early 50% tmax = Time to early half-maximal drug concentration; Late 50% tmax = Time to late half-maximal drug concentration; LS = Least squares; N = Number of patients; n = Number of observations; Onset of Appearance = Time from study drug administration until the first time serum insulin lispro concentrations reached the lower limit of quantification; tmax = time of maximum observed drug concentration
Model: PK = Period + Treatment + Patient + Random Error, where Patient is fitted as a random effect
The CIs for the ratio were calculated using the Fieller's theorem
P-value is for the test of the mean difference.

(Source: CSR for Study ITRW, Tables ITRW.7.2 and ITRW.7.3, pp 30, 32)

Pharmacodynamics:

Individual blood glucose concentrations following individualized insulin lispro dose of LYUMJEV or Humalog in T1DM patients are presented in Figure 19.

Figure 19 Individual and Mean Blood Glucose Concentration Following Individualized Doses of LYUMJEV or Humalog Before Meals or 20 Minutes Post-Meal in T2DM Patients



(Source: Reviewer generated graph)

Though there was a trend towards an earlier glucose-lowering effect and a lower postprandial glucose excursion over the complete 5-hour MMTT following administration of LYUMJEV compared to Humalog at both of the meal-to-dose timing intervals (immediately before the start of the test meal and 20 minutes following the start of the test meal), the differences did not reach statistical significance (Figure 19, Table 18).

Table 18 Statistical Analysis of the Change from Baseline in Glucodynamic Endpoints Following the Mixed Meal Tolerance Test of LYUMJEV Compared to Humalog in T1DM Patients

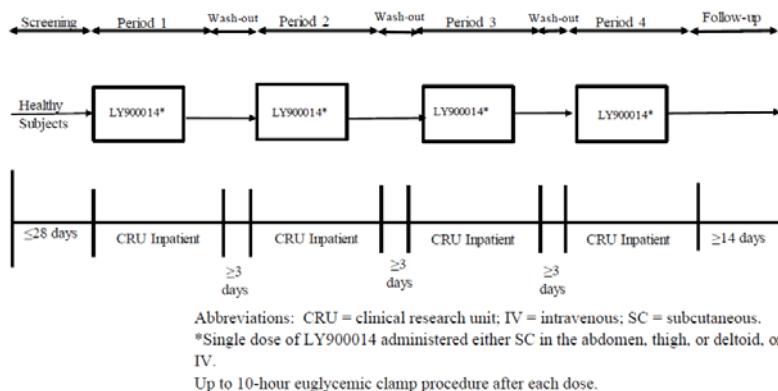
Parameter	Treatment	LS mean (N)	Difference in LS means (LY900014 - Humalog)	95% CI for the difference (Lower, Upper)	P-value	Ratio of LS means (LY900014 : Humalog)	95% CI for the ratio (Lower, Upper)
Glucose ΔAUC(0-5h) (mg.h/dL)	Humalog (0 min)	135.06 (34)	-34.08 (-34.08)	(-80.51, 12.36) (-86.67, 6.32)	0.1484 0.0895	0.75 0.74	(0.42, 1.16) (0.49, 1.01)
	LY900014 (0 min)	100.99 (34)					
	Humalog (+20 min)	151.96 (33)					
	LY900014 (+20 min)	111.78 (35)					
ΔBGmax (mg/dL)	Humalog (0 min)	67.21 (35)	-12.53 (-12.53)	(-22.17, -2.89) (-20.27, -0.99)	0.0113 0.0310	0.81 0.87	(0.68, 0.97) (0.77, 0.98)
	LY900014 (0 min)	54.68 (35)					
	Humalog (+20 min)	79.79 (35)					
	LY900014 (+20 min)	69.16 (35)					

(Source: CSR for Study ITRW, Table ITRW.7.9, pp 44, -46)

Study ITRT: Absolute bioavailability of LYUMJEV Following intravenous injection and relative bioavailability following administration into abdomen, deltoid or thigh during a 10-hour euglycemic clamp

The absolute bioavailability of insulin lispro following SC administrations of LYUMJEV into the thigh, deltoid, and abdomen compared to IV administration, and the relative bioavailability of insulin lispro from injection into the thigh and deltoid compared to the abdomen in healthy subjects was investigated in Study ITRT. This study was a Phase 1, single-center, open-label, 4-period, randomized, crossover, 10-hour euglycemic clamp study in healthy subjects to compare the insulin lispro PK and GD of LYUMJEV after SC administration of a 15-U dose at 3 different injection sites and a single IV bolus injection of 15 U.

A total of 28 healthy male subjects, aged between 24 and 63 years (mean = 39.8 years), participated in this study. The mean body weight was 70.1 kg and the mean BMI was 24.3 kg/m². A schematic of the study design is shown below:

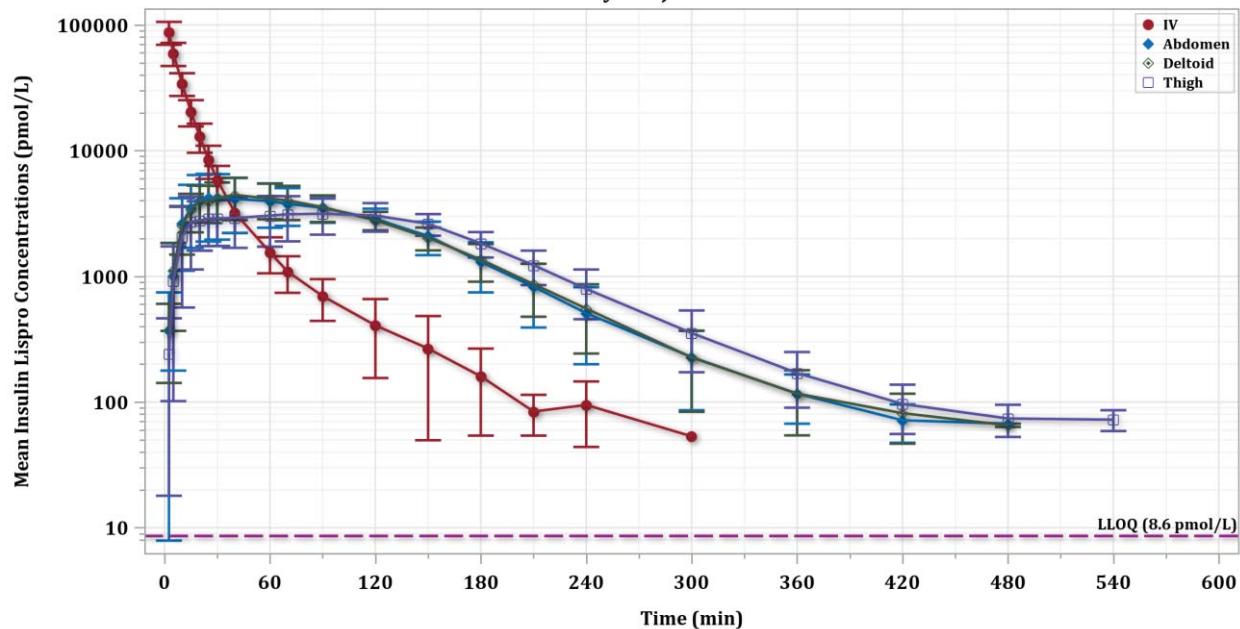


Serial blood samples were taken for the PK measurement of insulin lispro.

The mean insulin lispro concentrations following administration of single 15U doses of LYUMJEV, via intravenous, subcutaneously via abdomen, deltoid and thigh are shown in [Figure 20](#).

Figure 20 Mean (\pm SD) insulin lispro concentration versus time by injection site following single 15 U doses of LYUMJEV in Healthy Volunteers

Study ITRT: Effect of Injection Site on the Relative and Absolute Bioavailability of Single Dose of LYUMJEV in Healthy Subjects



(Source: Reviewer generated graph)

Absolute Bioavailability:

Following IV administration of LYUMJEV mean serum insulin lispro concentration appeared to decline in a biphasic manner after reaching C_{max} . The estimated $t_{1/2}$ was 0.73 hours, with an absolute CL of 32 L/h and V_z of 34 L.

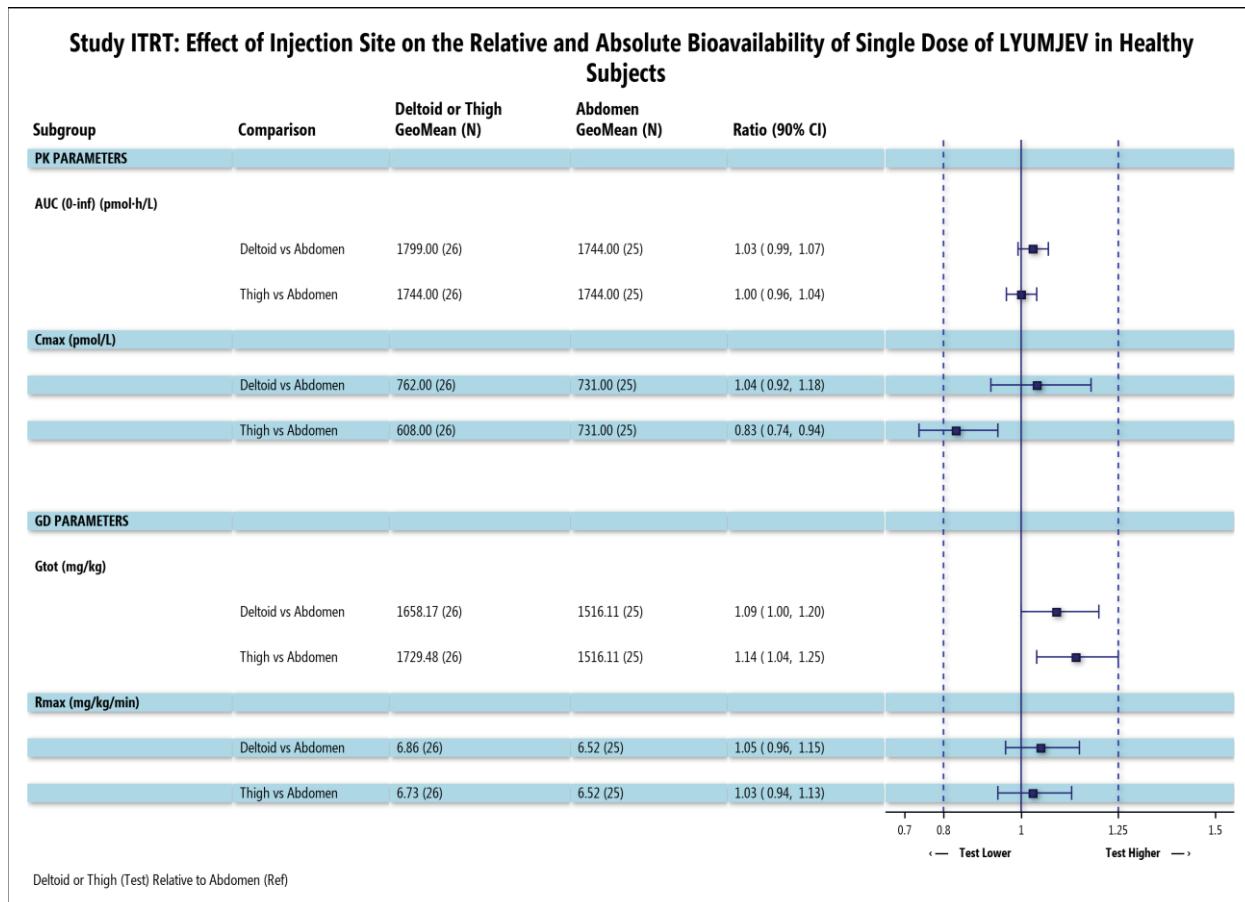
The absolute bioavailability following subcutaneous injection was nearly the same across abdomen, deltoid and thigh, with a bioavailability ranging between 64% to 65%.

Relative Bioavailability:

Comparison of $AUC_{(0-\infty)}$ between the thigh and abdomen, and deltoid and abdomen showed that the ratio of geometric LS means were 1.00 and 1.03, respectively. The 90% CI for the ratio overlapped 1 for both comparisons and was contained within 0.8 to 1.25 limits.

Mean C_{max} was slightly lower in the thigh compared to both the abdomen and deltoid. The ratio of the geometric LS means of C_{max} between abdomen and deltoid was 1.04, with the 90% CI including 1, and was maintained between 0.8 and 1.25. However, the ratio of the geometric LS means between the thigh and abdomen was less than 1, and the lower and upper 90% CI did not include 1, thus making this difference statistically significant (Figure 21).

Figure 21 Forest Plot of PK and GD Parameters Comparison of Injection Sites Following Single 15 U Subcutaneous Administration of LYUMJEV in Healthy Volunteers

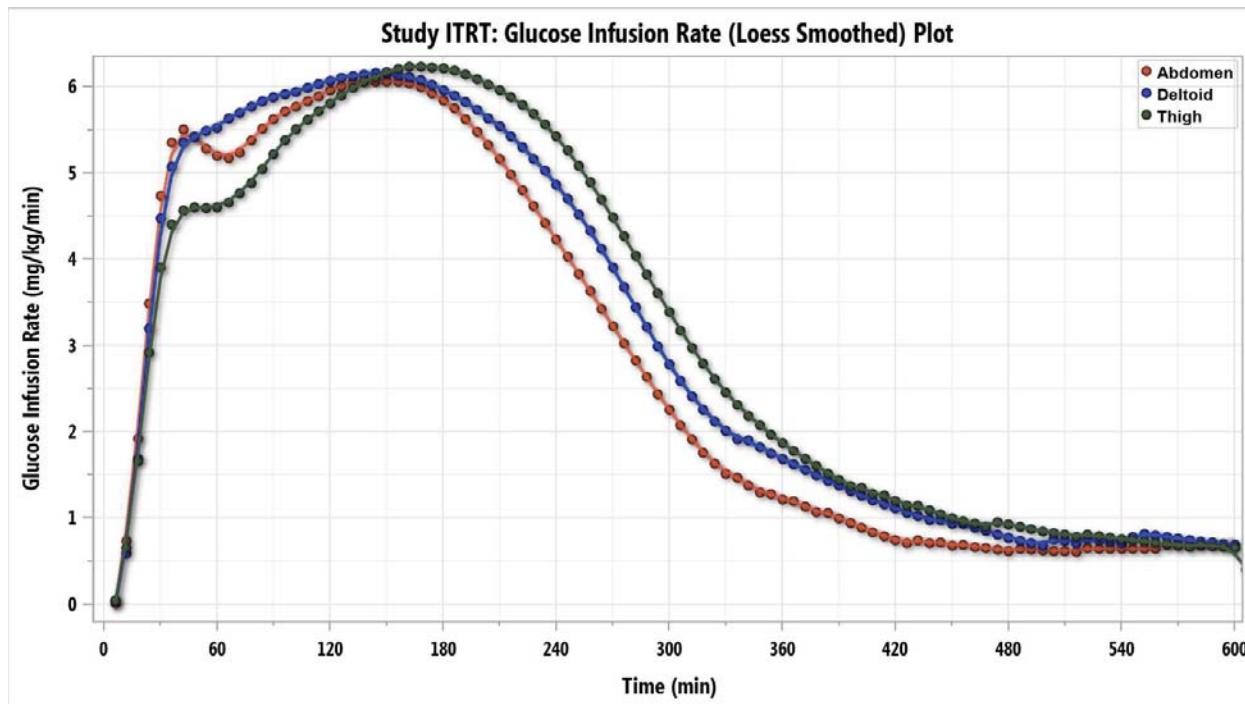


(Source: Reviewer generated graph)

Pharmacodynamics:

Mean LOESS fits of GIR versus time comparing administration of 15 U subcutaneous dose of LYUMJEV in the abdomen, deltoid and thigh are presented in [Figure 22](#).

Figure 22 Mean Glucose infusion Rate Comparison of Injection Sites Following Single 15 U Subcutaneous Administration of LYUMJEV in Healthy Volunteers



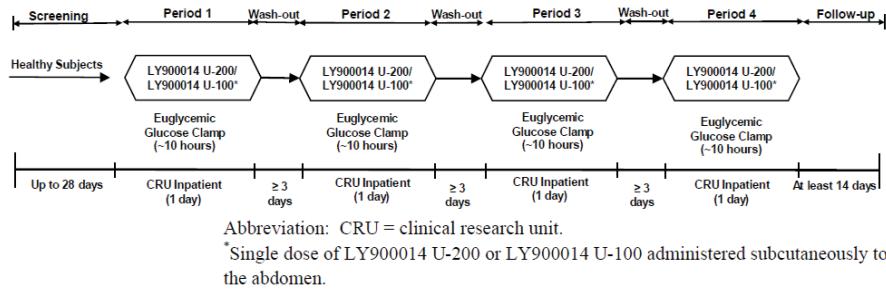
(Source: Reviewer generated graph)

The mean LOESS GIR profiles following SC injection of LYUMJEV into the abdomen, thigh, and deltoid, are comparable (Figure 22). There was no statistically significant difference between deltoid and abdomen in the GD parameters (G_{tot} and R_{max}), with the 90% CIs for the ratios of the LS means containing 1 for both comparisons and was contained within 0.8 to 1.25 (Figure 21). There was also no statistically significant difference between abdomen and thigh on R_{max} , but G_{tot} was slightly higher in the thigh. The 90% CIs for the ratios of the LS means between abdomen and thigh for both G_{tot} and R_{max} were contained within 0.8 to 1.25 (Figure 21).

Study ITSS: Relative bioavailability (BA) between the U-200 and U-100 formulations (PK and PD comparison)

The comparative pharmacokinetics and glucodynamics of two strengths of LYUMJEV, U-100 and U-200, were investigated in Study ITSS, a Phase 1, single-center, subject- and investigator-blind, randomized, 2-sequence, 4-period, crossover, 10-hour euglycemic clamp study in 68 healthy subjects.

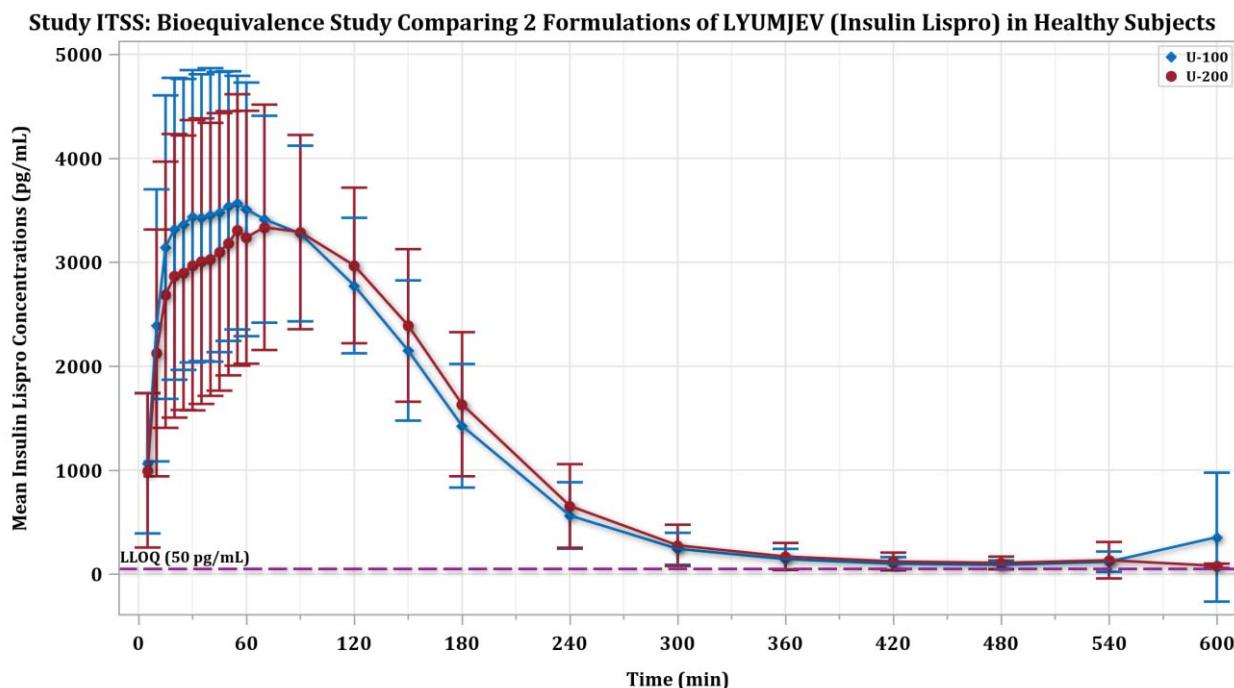
A total of 68 healthy subjects, 65 male and 3 female aged between 23 and 66 years (mean = 39.6 years), participated in this study. The mean body weight was 79.5 kg and the mean BMI was 24.4 kg/m². A schematic of the study design is shown below:



Serial blood samples were taken for the PK measurement of insulin lispro.

The mean insulin lispro concentrations following administration of single 15U subcutaneous doses of LYUMJEV U-100 and U-200 are shown in [Figure 23](#).

Figure 23 Mean (\pm SD) Insulin Lispro Concentration Versus Time Following Single 15 U Subcutaneous Doses of LYUMJEV U-200 and U-100 in Healthy Volunteers

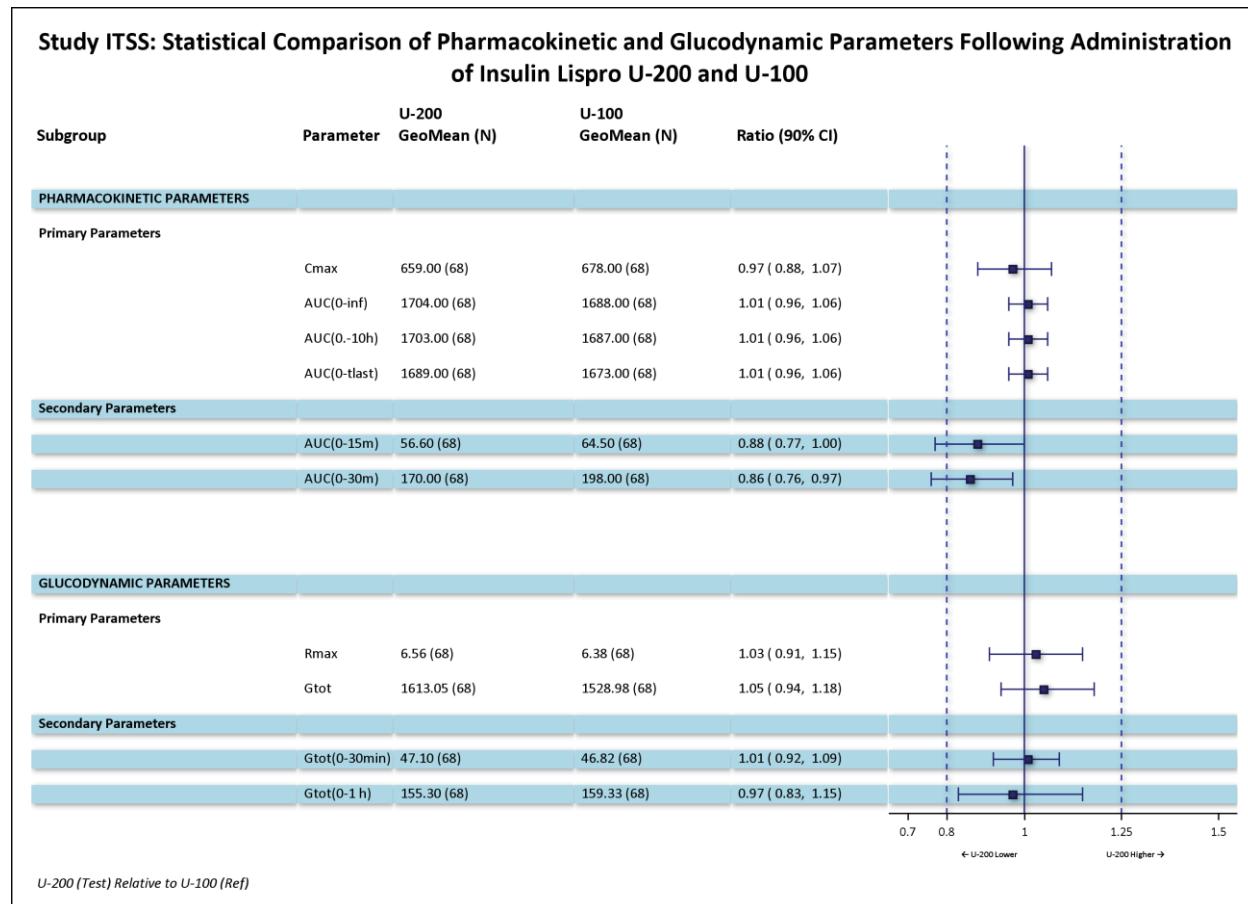


(Source: Reviewer generated graph)

Pharmacokinetics:

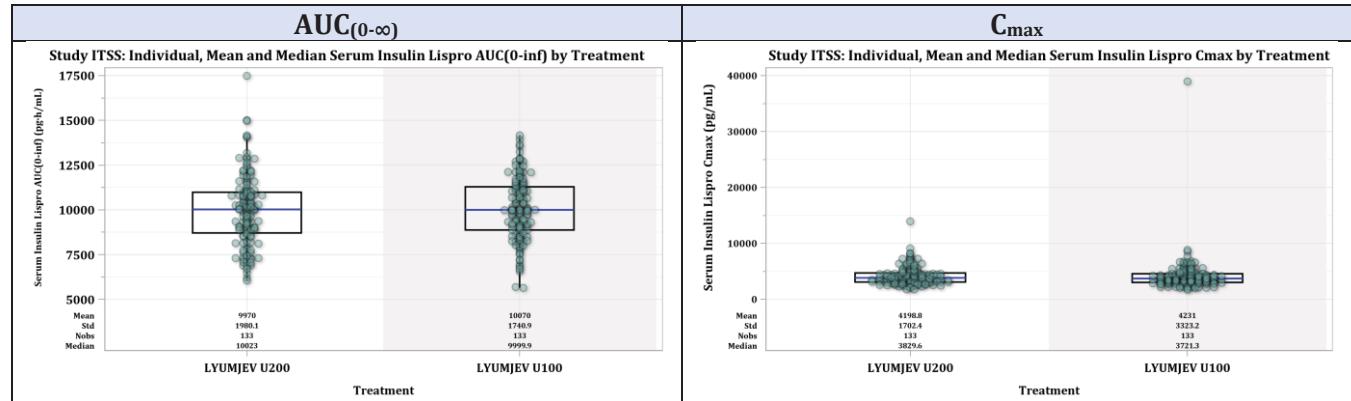
A comparison of the primary pharmacokinetic parameters for U-200 and U-100 showed that the ratios of U-200/U-100 were 1.01 for the $AUC_{(0-10h)}$, $AUC_{(0-tlast)}$, and $AUC_{(0-\infty)}$, and 0.97 for C_{max} . The 90% CIs for all the ratios were contained within the BE limits (0.80, 1.25) ([Figure 24](#)), demonstrating bioequivalence of U-200 versus U-100 formulations of LYUMJEV. Variability of $AUC_{(0-\infty)}$ and C_{max} were similar between U-200 and U-100 formulations ([Figure 25](#)).

Figure 24 Forest Plot of PK and GD Parameters Comparing U-200 and U-100 Formulations of LYUMJEV Following Single 15 U Subcutaneous Administration in Healthy Volunteers



(Source: Reviewer generated graph)

Figure 25 Comparison of PK Parameters for U-200 and U-100 Formulations of LYUMJEV Following Single 15 U Subcutaneous Administration in Healthy Volunteers

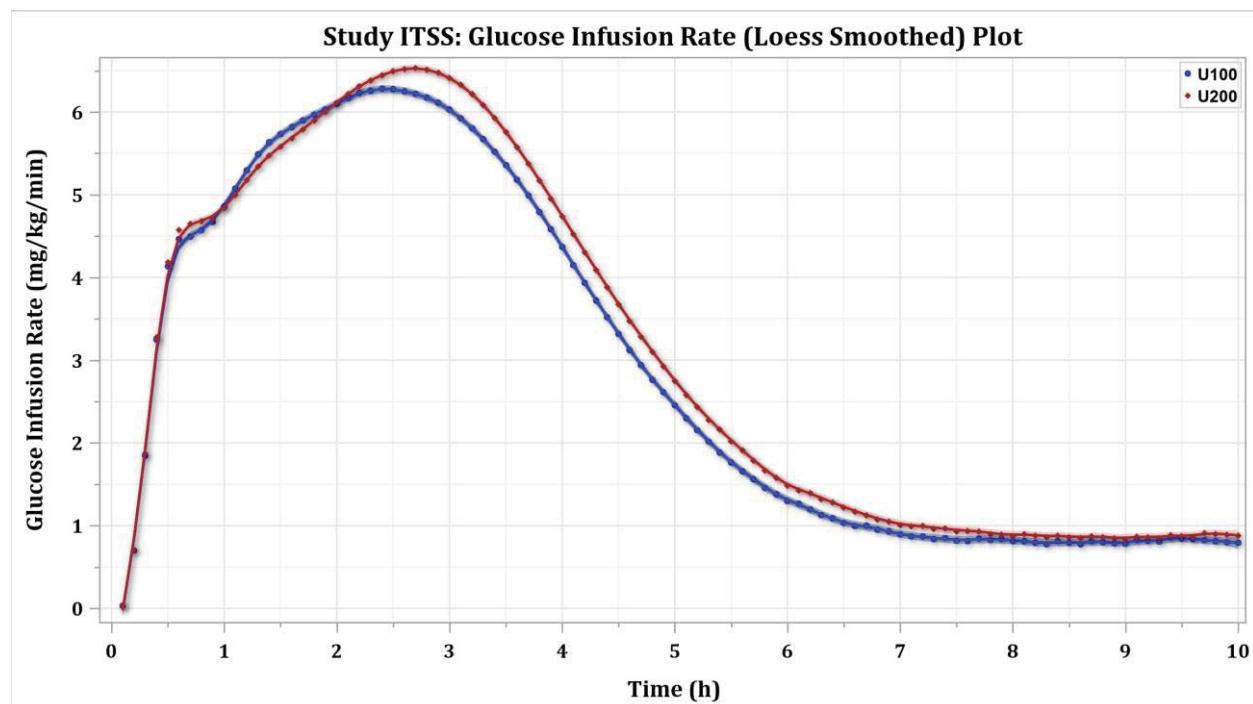


(Source: Reviewer generated graph)

Glucodynamics:

Comparable GIR versus time profiles were observed following administration of 15 U doses of LYUMJEV U-100 and U-200 formulations (Figure 26). Primary PD parameters for the two formulations were similar, as seen by the ratios (U200/U100) of geometric LS means of 1.05 for G_{tot} and 1.03 for R_{max} , and 90% CIs that were contained within the BE limits (0.80, 1.25) for both G_{tot} and R_{max} (Figure 24).

Figure 26 LOESS Smoothed Glucose Infusion Rate following single 15 U Subcutaneous Doses of LYUMJEV U-200 or U-100 in Healthy Volunteers



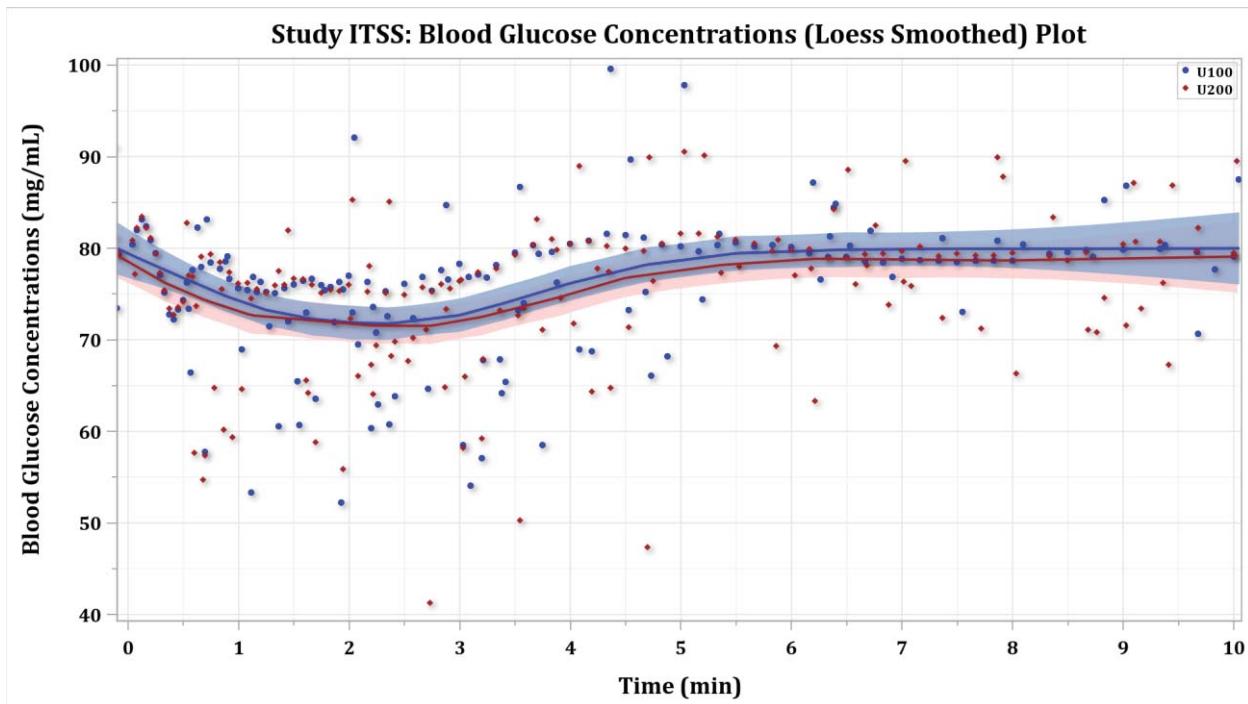
(Source: Reviewer generated graph)

The time to maximum glucose infusion rate, T_{Rmax} values were statistically significantly different with a median difference of approximately 16.5 minutes following administration of 15 U doses of LYUMJEV U-200 and U-100 formulations.

Early 50% t_{Rmax} (U-200: 27.2 minutes; U-100: 27.4 minutes) and T_{onset} (U-200: 21.9 minutes; U-100: 21.3 minutes) occurred at a similar time after administration of 15 U doses of U-200 and U-100 LYUMJEV. The early insulin action as measured by the amount of glucose infused in the first 30 minutes ($G_{tot[0-30min]}$) (U-200: 47.1 mg/kg; U-100: 46.8 mg/kg) and hour ($G_{tot[0-1h]}$) (U-200: 155.3 mg/kg; U-100: 159.3 mg/kg) of the clamp were similar.

Mean blood glucose concentrations during the euglycemic clamp were similar between the U-100 and U-200 formulations of LYUMJEV (Figure 27).

Figure 27 LOESS Smoothed Blood Glucose Concentrations following single 15 U Subcutaneous Doses of LYUMJEV U-200 or U-100 in Healthy Volunteers



(Source: Reviewer generated graph)

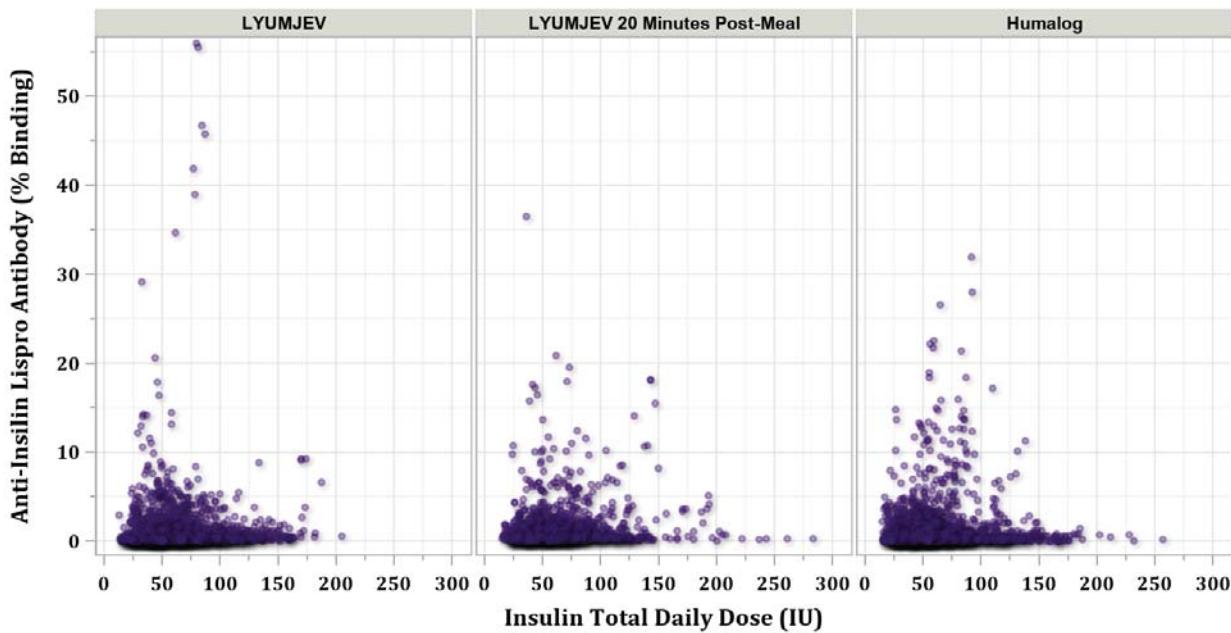
4.3 Immunogenicity

Based on the data from the open-label and double-blind treatment groups from Study ITRM (T1DM patients) and the data from Study ITRN (T2DM patients), the immunogenicity results for LYUMJEV were comparable to that of Humalog. The presence of treatment-emergent antidiug antibodies (TEADAs) did not cause a clinically meaningful effect on the efficacy or safety of LYUMJEV.

Approximately 33% of LYUMJEV-treated and 32% of Humalog-treated patients with T1DM developed TEADA after 26 weeks of treatment in the open-label and double-blind treatment groups of Study ITRM. After 52 weeks of treatment in the double-blind treatment groups of Study ITRM, 37% of LYUMJEV-treated and 34% of Humalog-treated patients with T1DM developed TEADA. The total daily insulin dose was similar between Humalog, LYUMJEV administered prior to meal and LYUMJEV administered 20 minutes post-meal ([Figure 28](#)).

Figure 28 Anti-Insulin Lispro Antibodies Versus Total Daily Insulin Dose in T1DM Patients

Study ITRM: LYUMJEV versus Humalog in Combination with Insulin Glargine or Insulin Degludec in T1DM Patients

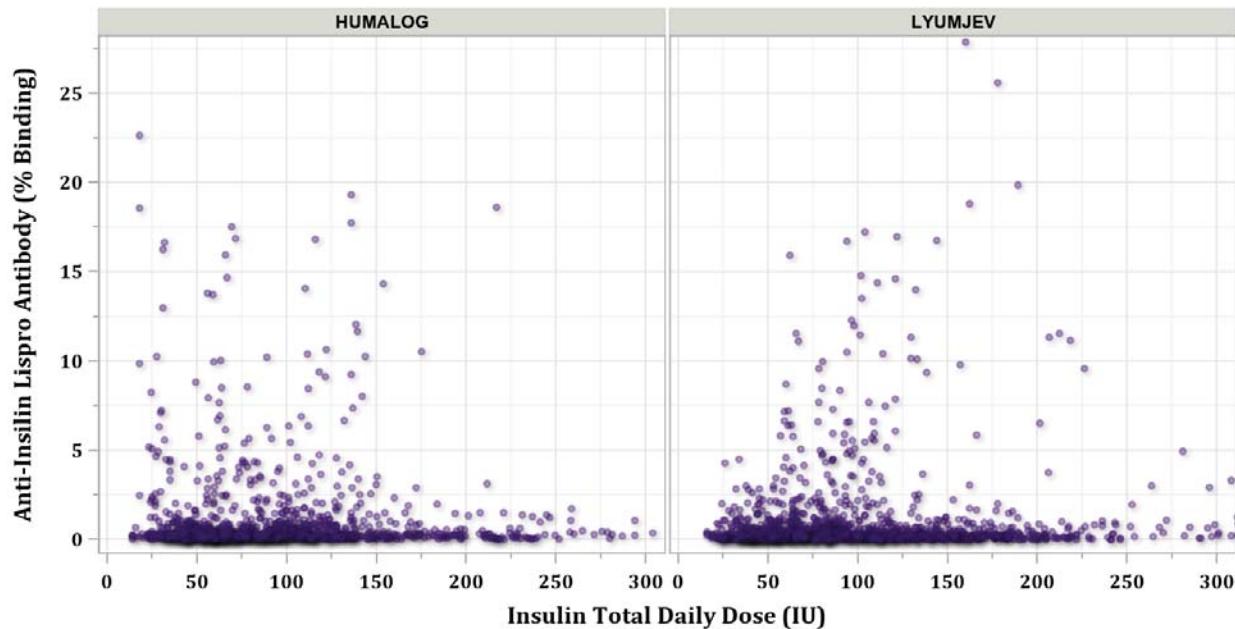


(Source: Reviewer generated graph)

Approximately 31% of LYUMJEV-treated and 24% of Humalog-treated patients with T2DM developed TEADA after 26 weeks of treatment in Study ITRN. Most patients who developed TEADA were cross reactive to native insulin and had low change in the percent bound tracer divided by total tracer counts ($\Delta\%B/T$) values, however, this did not affect the PK or GD profile of LYUMJEV as compared to Humalog. The total daily insulin dose was similar between Humalog and LYUMJEV administered prior to meal ([Figure 29](#)).

Figure 29 Anti-Insulin Lispro Antibodies Versus Total Daily Insulin Dose in T2DM Patients

Study ITRN: LYUMJEV versus Humalog in Combination with Insulin Glargine or Insulin Degludec in T2DM Patients



(Source: Reviewer generated graph)

Approximately 43% of patients in the Phase 3 and clinical pharmacology studies had antidrug antibody (ADA) present at baseline, possibly due to previous exposure to insulin therapy, including insulin lispro, and disease state (Table 19).

Table 19 Percent of Subjects and Patients with Detectable Anti-Insulin Lispro Antibodies at Baseline Across the Clinical Pharmacology Studies with LYUMJEV and Humalog

Study Population	Study ID	Not Detected	Detected	Percent Detected by Population
HS	ITRL ^a	31	0	1.3%
	ITRQ	49	0	
	ITRT	27	1	
	ITSH	41	1	
T1DM	ITRR	39	40	45%
	ITRV	24	12	
T2DM	ITRU	27	11	35%
	ITRW	21	15	
Total		259	80	24%

Abbreviations: ADA = anti drug antibody; HS = healthy subjects; T1DM = patients with type 1 diabetes; T2DM = patients with type 2 diabetes.

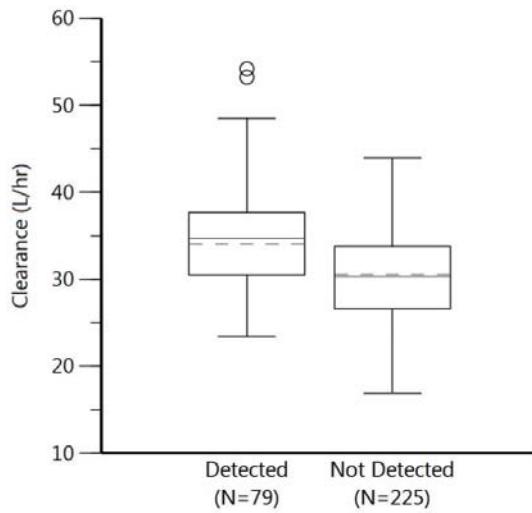
^a One subject did not have any reported ADA data.

(Source: Population PK/PD Report, Table 8.8, Page 100)

In the population PK analysis, baseline ADA status was one of the covariates identified on insulin lispro clearance however, it explained only about 4.6% of inter-individual variability. The 16.5% increase in insulin lispro clearance observed in patients who were ADA positive at baseline (Figure 30) is unlikely to produce any clinical meaningful difference in the PK of LYUMJEV, since insulins are individually

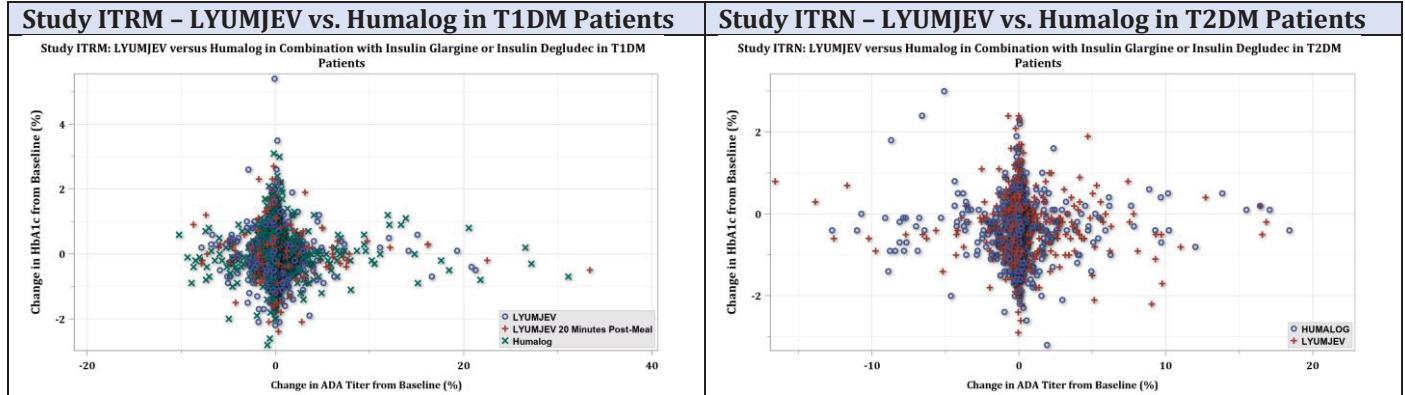
titrated. Baseline ADA status did not impact the PK or GD time-action profile of LYUMJEV compared to Humalog and did not have any effect on HbA1c in the Phase 3 trials in T1DM and T2DM patients. A plot of change in HbA1c from baseline versus change in ADA titer from baseline did not show any correlation in T1DM or T2DM patients (Figure 31).

Figure 30 Box-Plot of Post-Hoc Clearance in Insulin Lispro Stratified by Anti-Insulin Lispro Antibody Status at Baseline in Clinical Pharmacology Studies with LYUMJEV and Humalog



(Source: Population PK/PD Report, Figure 8.33, Page 101)

Figure 31 Change from Baseline in HbA1c versus Change from Baseline in ADA Titer in T1DM and T2DM Patients



(Source: Reviewer generated graph)

Since the active ingredient in LYUMJEV and Humalog is the same insulin lispro, factors related to the diabetes patient population or route of administration are not expected to change the risk of immunogenicity after LYUMJEV administration compared to Humalog. No clinically meaningful association was observed between immunogenicity and drug exposure, efficacy, or risk of adverse events for LYUMJEV in the Phase 3 and Clinical Pharmacology trials.

The acceptability of the immunogenicity data and associated analytical method is further deferred to the OBP review.

4.4 Pharmacometrics Assessment

4.4.1 Executive Summary

The PK of insulin lispro after IV or SC administration of LYUMJEV in healthy subjects, and patients with T1DM or T2DM was well characterized by a three-compartment model, with a combined zero-order and first-order absorption model incorporating transit compartments for the SC administration of LYUMJEV. Body weight was included in the population PK model as a significant covariate on insulin lispro clearance and volume of distribution using allometric scaling principles. However, dose adjustment for LYUMJEV is recommended based on clinical response and meal intake. Therefore, explicitly dosing based on body weight is not necessary. No additional patient factors (i.e., age, race, sex, renal function, etc.) were identified to impact the insulin lispro PK exposures.

The Applicant's modified IGI model developed for patients with T1DM solely based on Phase 1 Trial ITRV predicted slightly larger difference in PPG excursion and smaller difference in the incidences of all documented hypoglycemia for LYUMJEV administered 20 min post meal compared to Humalog pre-meal than that observed in Phase 3 Trial ITRM. This is probably because: 1) the test meal was well controlled in Phase 1 Trial ITRV versus that uncontrolled in the Phase 3 Trial ITRM, 2) Trial ITRV was a single dose trial versus a 52-week multiple dose trial for ITRM, and 3) the lack of individual carbohydrate consumption and insulin PK data in Trial ITRM limited the IGI model's capacity of producing accurate simulation for the incidences of all documented hypoglycemia in patients with T1DM.

The Applicant's modified IGI model developed for patients with T2DM based on Phase 1 Trial ITRW well predicted lower PPG excursion and generally similar incidences of all documented hypoglycemia for LYUMJEV compared to Humalog as observed in Phase 3 Trial ITRN when both insulins were given prior to the start of a meal. The model also predicted generally comparable PPG excursion and incidences of all documented hypoglycemia in patients with T2DM for LYUMJEV administered 20 min post meal compared to Humalog pre-meal, which supports the proposed administration of LYUMJEV within 20 minutes after starting a meal in patients with T2DM.

4.4.2 Population PK Analysis

PK Data

Population PK analysis was conducted based on 18957 evaluable insulin lispro concentrations in 338 subjects (149 healthy subjects, 115 patients with T1DM, and 74 patients with T2DM) from 8 trials (I8B-MC-ITRL, I8B-MC-ITRT, I8B-MC-ITRR, I8B-MC-ITRU, I8BMC-ITS, I8B-MC-ITRQ, I8B-MC-ITRV, and I8B-MC-ITRW). Study design, subject populations, treatment arms, dosing regimens, and route of administration of the 8 clinical trials are summarized in [Table 20](#).

Table 20 Summary of Study Design, Populations, Doses and Routes of Administration

Study Alias	Description	Population	Glucodynamics	Treatment Arms	Dose (U)	Route of Administration	Number of Patients/Subjects
ITRL	2-period crossover study evaluating PK and GD of LY900014 and Humalog during an 8-hour euglycemic clamp	Healthy subjects	Euglycemic glucose clamp	LY and Humalog	15	SC	32
ITRQ	Bioequivalence study comparing the PK and GD of 200 U/mL LY900014 formulation with 100 U/mL LY900014 formulation	Healthy subjects	Euglycemic glucose clamp	LY 100 units/mL and 200 units/mL	15	SC	49
ITRR	2-period crossover study evaluating PK and GD of LY900014 and Humalog during a 10-hour automated clamp	Young (18 to 45 years inclusive) and elderly (≥ 65 years) T1DM	Euglycemic glucose clamp	LY and Humalog	15	SC	79
ITRT	Absolute and relative bioavailability study comparing the PK and GD of insulin lispro following 15-U dose of LY900014 administered IV and SC into the thigh, deltoid or abdomen	Healthy subjects	Euglycemic glucose clamp	LY	15	IV and SC	28
ITRU	2-period crossover study evaluating PK and GD LY900014 and Humalog during a 10-hour automated clamp	T2DM	Euglycemic glucose clamp	LY and Humalog	15	SC	38
ITSH	6-period crossover study evaluating PK and GD of LY900014 and Humalog during a 10-hour euglycemic clamp	Healthy subjects	Euglycemic glucose clamp	LY and Humalog	7, 15, 30	SC	42
ITRV	4-period crossover MMTT study evaluating PK and GD of LY900014 and Humalog administered immediately before and 20 minutes after the start of a test meal	T1DM	MMTT	LY and Humalog	Individualized (6 – 34) ^a	SC	36
ITRW	4-period crossover MMTT study evaluating PK and GD of LY900014 and Humalog administered immediately before and 20 minutes after the start of a test meal	T2DM	MMTT	LY and Humalog	Individualized (5 – 40) ^a	SC	36

(Source: Applicant's Population PK/PD Report Table 7.1.)

Summary statistics of the evaluated covariates in the population PK analysis are shown in [Table 21](#). The subjects had a median (range) age of 46.5 (18, 77) years, and were primarily White (68%) and Asian (31%). There were 284 (84.0%), 50 (14.8%), 3 (0.9%) and 1 (0.3%) patients with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment, respectively, according to their creatinine clearance calculated using the Cockcroft-Gault Equation.

Table 21 Demographics (Median [Range]) at Study Entry for Patients Included in the Pharmacokinetic Analysis

Study	N	Age (yr)	Body Weight (kg)	Waist Circumference (cm)	Waist/Hip Ratio	Race N (%)	Sex N (%)		GFR (mL/min)
						F	M		
Healthy Subjects									
ITRL	31	38 (22-60)	65.4 (49.5-90.1)	NR	NR	Asian 31 (100)	3 (9.7)	28 (90.3)	101.1 (21 ^a -173)
ITRT	27	38 (24-63)	68.9 (53.2-90.3)	87.0 (75.0-98.1)	0.90 (0.84-0.99)	Asian 27 (100)	--	27 (100)	102.4 (68-182)
ITSH	42 ^b	43 (18-60)	76.5 (55.6-114.5)	86.2 (69.4-110.3)	0.91 (0.74-1.05)	White 40 (95.2) AmIndian/AKNat 2 (4.8)	15 (35.7)	27 (64.3)	117.5 (70-197)
ITRQ	49	38 (27-61)	73.3 (48.6-95.9)	86.2 (68.0-105.6)	0.90 (0.76-1.04)	White 2 (4.1) Asian 47 (95.9)	5 (10.2)	44 (89.8)	124.4 (83-188)
All	149	38 (18-63)	72.8 (48.6-114.5)	86.4 (69.4-110.3)	0.90 (0.74-1.05)	White 42 (28.2) Asian 105 (70.5) AmIndian/AKNat 2 (1.3)	23 (15.4)	126 (84.6)	115.9 (21-197)
Type 1 Diabetes Mellitus									
ITRR	79	44 (22-77)	79.0 (52.6-102.6)	92.3 (70.7-114.5)	0.91 (0.74-1.32)	White 79 (100)	29 (36.7)	50 (63.3)	112.7 (49-213)
ITRV	36	47 (23-69)	79.6 (52.0-107.4)	94.2 (70.3-111.5)	0.92 (0.78-1.26)	White 35 (97.2) Multiple 1 (2.8)	9 (25)	27 (75)	126.4 (78-187)
All	115	46 (22-77)	79.3 (52.0-107.4)	92.9 (70.3 – 114.5)	0.91 (0.74-1.32)	White 114 (99.1) Multiple 1 (0.9)	38 (33.0)	77 (67.0)	122.3 (49-213)
Type 2 Diabetes Mellitus									
ITRU	38	61 (38-70)	95.6 (62.8-117.1)	107.7 (81.6-125.1)	1.02 (0.87-1.16)	White 38 (100)	3 (7.9)	35 (92.1)	122.4 (72-196)
ITRW	36	63 (48-70)	96.9 (74.0-141.5)	112.7 (89.7-134.2)	1.03 (0.90-1.14)	White 36 (100)	5 (13.9)	31 (86.1)	112.1 (71-219)
All	74	61 (38-70)	96.4 (62.8-141.5)	110.1 (81.6-134.2)	1.03 (0.87-1.16)	White 74 (100)	8 (10.8)	66 (89.2)	117.8 (71-219)
Overall									
All	338	46.5 (18-77)	78.9 (48.6-141.5)	95.2 (69.4-134.2)	0.95 (0.74-1.32)	White 230 (68.0) Asian 105 (31.1) AmIndian/AKNat 2 (0.6) Multiple 1 (0.3)	69 (20.4)	269 (79.6)	117.7 (21-219)

Abbreviations: AmIndian/AKNat = American Indian/Alaska native; F = female; GFR = glomerular filtration rate (calculated using Cockcroft-Gault creatinine clearance); M = male; N = number of patients; NR = not reported.

a Subject (b) (6) (Study ITRL) had baseline serum creatinine value of 359 umol/L which was repeated 10 hours later and reported as 82 umol/L. The first value was captured in the NONMEM dataset and was used for calculation of the GFR for this subject.

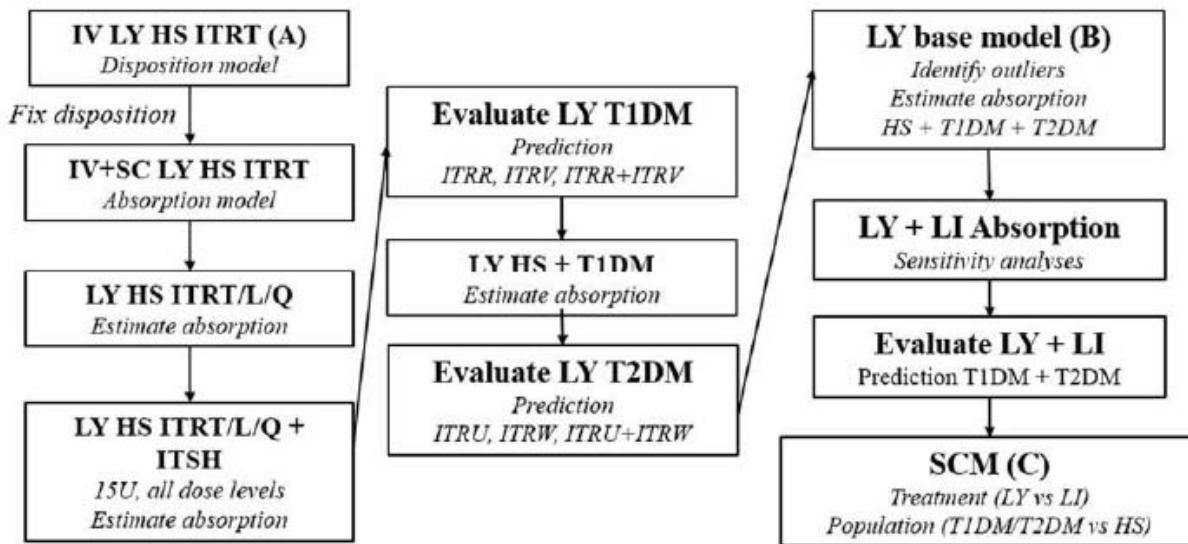
b Subject (b) (6) and Subject (b) (6) (Study ITSH) provided only limited data (15U for Humalog, and 15U + 30U for LY900014, respectively). Thus, only 41 subjects provided data for both Humalog and LY900014.

(Source: Applicant's Population PK/PD Report Table 7.1.)

Methods

The Applicant used a step-wise approach to develop the meta population PK model. Data from the different studies were added sequentially, ranked according to information content. The workflow for the development process is shown in Figure 32. First, a base model (Model A) was developed to characterize the disposition and absorption of insulin lispro in healthy subjects using data for LYUMJEV only. The base model was then evaluated and updated with more insulin lispro data for LYUMJEV from patients with T1DM or T2DM. Subsequently, the base model (Model B) was developed by re-estimating all the absorption parameters with all the available insulin lispro data following LYUMJEV administration in healthy subjects and patients with T1DM or T2DM. Sensitivity analyses were performed to select the appropriate insulin lispro absorption parameters to assess treatment differences (LYUMJEV vs Humalog). Stepwise covariate modeling (SCM) building was used for this assessment. The model (Model C) incorporating the treatment and population differences was considered as the final model after confirmed by the final backwards deletion using SCM approach.

Figure 32 General Process for Pharmacokinetic Model Development



Abbreviations: IV – intravenous; LY = LY900014; HS = healthy subjects; SC = subcutaneous; T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, LI = Humalog, SCM = step-wise covariate model building

(Source: Applicant's Population PK/PD Report Figure 7.1.)

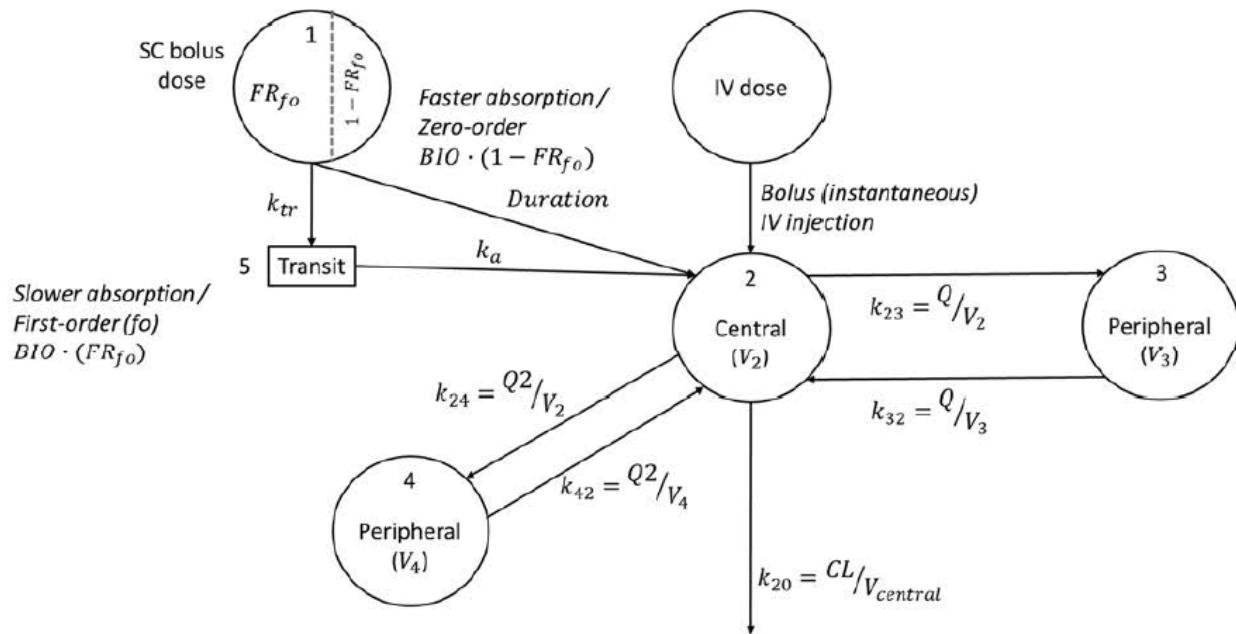
Model development was performed using first-order conditional estimation (FOCE) method with NONMEM (version 7.4) and PsN (version 4.2.0). Goodness-of-fit plots and data visualization was performed using R-software (version 3.2.2) using Xpose4 or ggplot2 packages.

Selection of the most appropriate base model was based upon: 1) convergence of the estimation and covariance routines, 2) parameter and variance estimates, 3) precision of the parameter and variance estimates, 4) shrinkage estimates of inter-patient variance terms, and 5) graphical evaluation of model misspecification.

Results

The PK of insulin lispro following IV and SC administration of LYUMJEV and SC administration of Humalog in patients with T1DM or T2DM and healthy subjects was best characterized by a three-compartment model with linear elimination, and a mixed zero-order absorption and first-order absorption via transit compartments ([Figure 33](#)).

Figure 33 Insulin Lispro IV and SC Structural Model following LYUMJEV Administration



Abbreviations: V_x = volume of distribution for compartment x; CL = clearance; Q_x = intercompartmental clearance for compartment x; k_{xy} = first-order rate constant from compartment x to y; IV = intravenous; SC = subcutaneous; FR = fraction; fo = first-order; BIO = bioavailability; k_{tr} = transit rate constant; k_a = first-order absorption constant.

(Source: Applicant's Population PK/PD Report Figure 8.7.)

Fraction absorbed via transit compartments (FR_{fo}) and first-order absorption rate constant (K_a) were estimated differently for LYUMJEV and Humalog, while bioavailability (BIO), K_a, central volume of distribution following SC administration (V_{2_SC}) and duration of zero-order absorption (DUR) were estimated separately for different subject populations (healthy subjects, patients with T1DM or T2DM). The modified insulin lispro PK model parameter estimates, along with the corresponding estimates of precision (95% CI) from Bootstrap are presented in Table 22. The interpretation of the clinically relevant differences between healthy subjects, patients with T1DM and patients with T2DM, and between LYUMJEV and Humalog are summarized in Table 23.

The goodness-of-fit plots in Figure 34 and the visual predictive checks (VPCs) in Figure 35 for the modified model stratified by treatment (LYUMJEV or Humalog®) and population (healthy subjects, patients with T1DM or T2DM) illustrated that the modified PK model generally maintained fidelity with the observed insulin lispro data.

Table 22 Pharmacokinetic Parameters for Insulin Lispro Model Following Subcutaneous Administration of LYUMJEV and Humalog®

Parameter		Estimate (%RSE)		% Variability (%RSE)		Bootstrap median	Bootstrap 95%CI		Bootstrap median	Bootstrap 95%CI
Clearance (CL) (L/h)	Θ_1	28.6 fix ^a	$\omega_{1,1}$	15.6 fix ^b	Θ_1	N/A	N/A	$\omega_{1,1}$	N/A	N/A
Central volume IV (V2_IV) (L)	Θ_2	4.73 fix ^a	$\omega_{2,2}$	6.25 fix ^a	Θ_2	N/A	N/A	$\omega_{2,2}$	N/A	N/A
Central volume SC (V2_SC) (L)	Θ_9	17.4 (4.7)	$\omega_{5,5}$	43.0 (5.8)	Θ_9	17.3	14.9, 20.9	$\omega_{5,5}$	45.4	38.0, 54.7
Intercompartmental clearance 1 (Q) (L/h)	Θ_3	3.89 fix ^a	$\omega_{6,6}$	14.8 fix ^a	Θ_3	N/A	N/A	$\omega_{6,6}$	N/A	N/A
Peripheral volume 1 (V3) (L)	Θ_4	1.49 fix ^a	$\omega_{7,7}$	24.6 fix ^a	Θ_4	N/A	N/A	$\omega_{7,7}$	N/A	N/A
Fraction absorbed via transit compartments (FR _{f0})	Θ_5	0.872 fix ^b	$\omega_{9,9}$	0 fix	Θ_5	N/A	N/A	$\omega_{9,9}$	0 fix	N/A
Mean transit time (MTT) (h)	Θ_6	1.18 (3.4)	$\omega_{3,3}$	50 (8.3)	Θ_6	1.19	1.02, 1.39	$\omega_{3,3}$	53.5	44.0, 72.7
Duration of zero-order absorption (DUR) (h)	Θ_7	0.239 (4.0)	$\omega_{4,4}$	42.2 (7.6)	Θ_7	0.239	0.213, 0.261	$\omega_{4,4}$	44.1	35.3, 100
Bioavailability (BIO)	Θ_8	0.542 (1.7)	$\omega_{8,8}$	31.4 (11.1)	Θ_8	0.544	0.519, 0.576	$\omega_{8,8}$	32.7	22.8, 42.4
First-order absorption rate constant (K_a) (h ⁻¹)	Θ_{10}	2.63 (14.3)	$\omega_{10,10}$	78.7 (8.2)	Θ_{10}	2.63	2.03, 4.09	$\omega_{10,10}$	92.5	77.5, 114
Intercompartmental clearance 2 (Q2) (L/h)	Θ_{11}	1.73 fix ^a	$\omega_{11,11}$	12.5 fix ^a	Θ_{11}	N/A	N/A	$\omega_{11,11}$	N/A	N/
Peripheral volume 2 (V4) (L)	Θ_{12}	2.0 fix ^a	$\omega_{12,12}$	8.0 fix ^a	Θ_{12}	N/A	N/A	$\omega_{12,12}$	N/A	N/A
Differences in Humalog® relative to LY900014										
Fraction absorbed via transit compartments	Θ_{13}	0.14 fix		N/A	Θ_{13}	N/A	N/A		N/A	N/A
First-order absorption rate constant (K_a) (h ⁻¹)	Θ_{14}	-0.597 (25.1)		N/A	Θ_{14}	-0.597	-0.698, -0.540		N/A	N/A
Differences in diabetics relative to healthy subjects										
Bioavailability for T1DM	Θ_{15}	-0.222 (9.8)		N/A	Θ_{15}	-0.226	-0.297, -0.166		N/A	N/A
Bioavailability for T2DM	Θ_{16}	-0.0131 (224)		N/A	Θ_{16}	-0.012	-0.09, 0.0617		N/A	N/A
First-order absorption rate constant for T1DM (K_a) (h ⁻¹)	Θ_{17}	1.15 (27.5)		N/A	Θ_{17}	1.18	0.833, 1.76		N/A	N/A
First-order absorption rate constant for T2DM (K_a) (h ⁻¹)	Θ_{18}	0.745 (36.9)		N/A	Θ_{18}	0.742	0.312, 1.3		N/A	N/A
Central volume SC for T1DM (L)	Θ_{19}	0.302 (29.3)		N/A	Θ_{19}	0.31	0.115, 0.570		N/A	N/A
Central volume SC for T2DM (L)	Θ_{20}	0.935 (15.8)		N/A	Θ_{20}	0.934	0.618, 1.32		N/A	N/A
Duration of zero-order absorption T1DM (h)	Θ_{21}	0.296 (28.3)		N/A	Θ_{21}	0.295	0.154, 0.519		N/A	N/A
Duration of zero-order absorption T2DM (h)	Θ_{22}	0.343 (28.3)		N/A	Θ_{22}	0.386	0.256, 0.734		N/A	N/A
Proportional error (%)	$\delta_{1,1}$	34.2 (1.1)		N/A	$\delta_{1,1}$	34.2	32.5, 35.8		N/A	N/A

Abbreviations: %RSE = relative standard error of the estimate as a percentage; CI = confidence interval; N/A = not appropriate, IV = intravenous administration route; SC = subcutaneous administration route.

^a Parameter values were fixed to the estimates from the IV model for LY900014.

^b Parameter values were fixed to the estimates from the IV+SC model for LY900014.

(Source: Applicant's Population PK/PD Report Table 8.4.)

Table 23 Covariate-Parameter Relationships for Differences Between LYUMJEV vs Humalog® and Healthy Subjects versus Patients with T1DM or T2DM

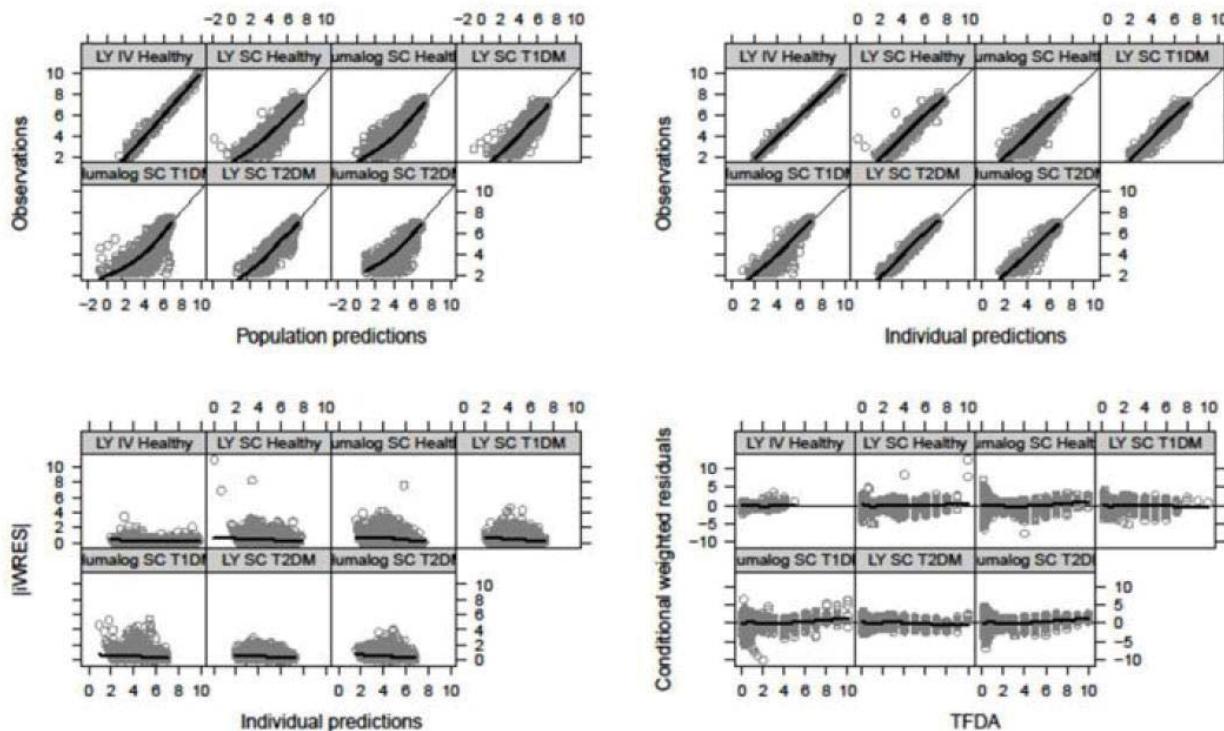
Covariate	PK attribute	PK parameters	Estimand	Median (95%CI) Change in PK parameters ^a
Differences between LY900014 and Humalog®	Absorption rate	Rate of absorption via transit compartments (K_a)	Θ_{14}	LY900014 absorbed 40% (30-46%) faster
		Fraction absorbed via transit compartments (FR_{fo})	Θ_{13}	100% for Humalog®
			Θ_5	87.2% for LY900014
Differences between healthy subjects and T1DM or T2DM subjects	Extent of absorption	SC bioavailability relative to IV LY900014 in HS (BIO)	Θ_{15}	22% (17 – 30%) lower in T1DM compared to HS
	Absorption rate	Rate of absorption via transit compartment compared to HS (K_A)	Θ_{16}	Similar for T2DM and HS
		Duration of zero-order absorption compared to HS (DUR)	Θ_{17}	118% (83 – 176%) faster in T1DM
			Θ_{18}	74% (31 – 130%) faster in T2DM
	Volume of distribution	Central volume of distribution for SC administration compared to HS (V_2_SC)	Θ_{21}	30% (15 – 52%) longer in T1DM
			Θ_{22}	39% (26 – 73%) longer in T2DM
			Θ_{19}	31% (12 – 57%) increase in T1DM
			Θ_{20}	93% (62 – 132%) increase in T2DM

Abbreviations: CI = confidence interval; DUR = duration of zero-order absorption; F = bioavailability; FR = fraction absorbed; HS = healthy subjects; IV = intravenous administration; KA = rate of absorption; PK = pharmacokinetic; SC = subcutaneous administration; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; V2_SC = central volume of distribution.

a Median and 95% confidence interval based on bootstrap evaluation.

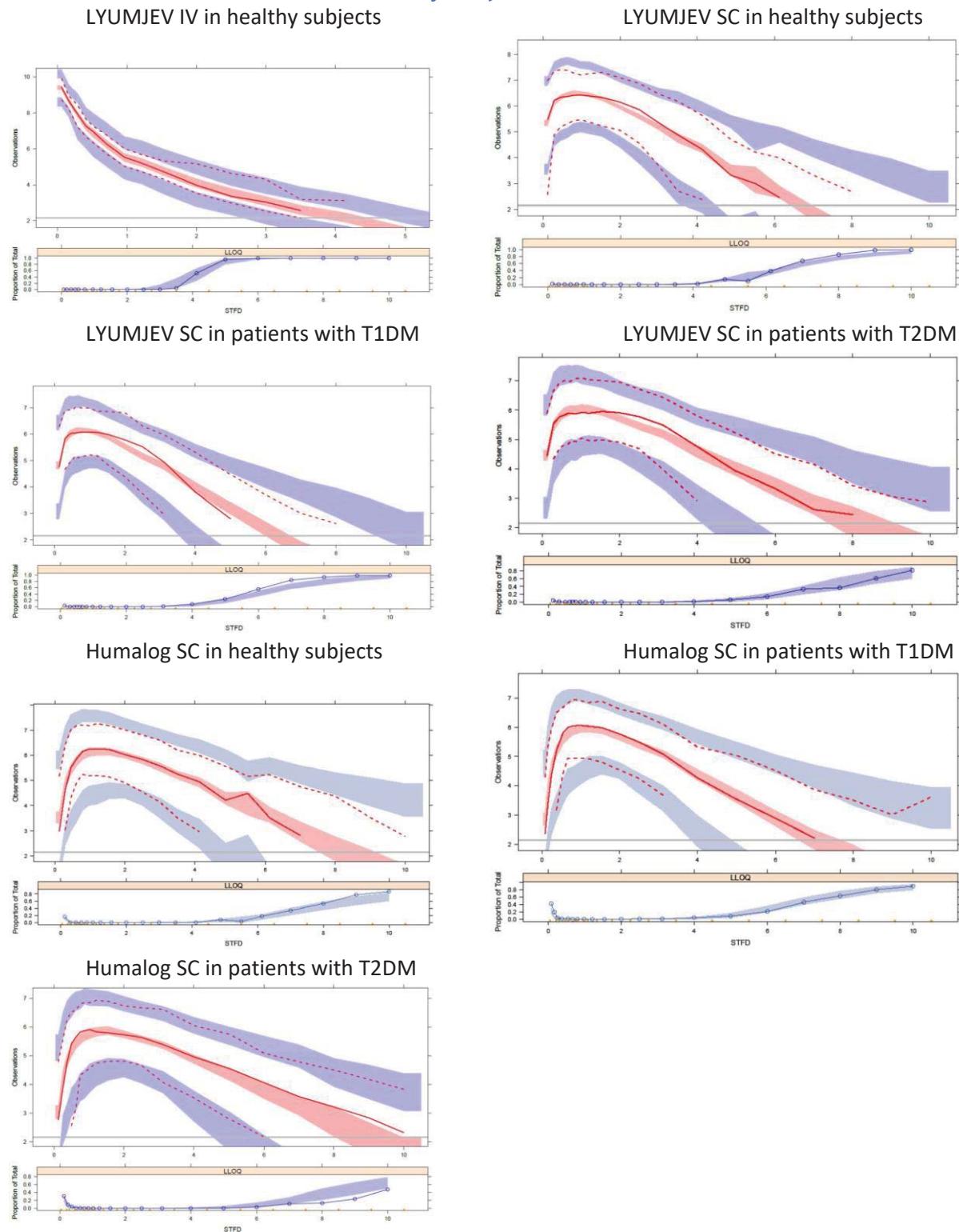
(Source: Applicant's Population PK/PD Report Table 8.5.)

Figure 34 Goodness-of-fit Plots for the Final Population PK Model Predictions of Serum Insulin Lispro Concentration following IV and SC LYUMJEV or SC Humalog Administration in Healthy Subjects and Patients with T1DM or T2DM



(Source: Applicant's Population PK/PD Report Attachment 3.12)

Figure 35 Visual Predictive Checks of the Final Population PK Model Predictions of Serum Insulin Lispro Concentration following IV and SC LYUMJEV or SC Humalog Administration in Healthy Subjects and Patients with T1DM or T2DM



(Source: Applicant's Population PK/PD Report Figures 8.8, 8.9, 8.10, 8.11, 8.12, 8.13 and 8.14.)

Reviewer's Comments:

The Applicant's population PK model appears adequate to describe the observed serum insulin lispro concentration-time profile following IV and SC LYUMJEV or SC Humalog administration in healthy subjects and patients with T1DM or T2DM. Therefore, the PK model is acceptable to simulate serum insulin lispro concentrations for E-R analyses for efficacy and safety measurements.

Body weight was included in the population PK model as a significant covariate on the clearance and volume parameters of the insulin lispro PK using allometric scaling principles. However, dose adjustment for insulin products are based on clinical response and specifically for prandial insulins, meal intake is also taken in consideration. Therefore, an explicit instruction or recommendation of dose adjustment for LYUMJEV based on body weight is not necessary. In addition, covariate analysis indicated that insulin lispro exposure was not significantly altered by age (18 years to 77 years), race (White or Asian), sex, mild renal impairment ($CL_{CR} \geq 60$ mL/min to <90 mL/min as estimated by Cockcroft-Gault equation), thus no dose adjustment is needed for the above-mentioned specific populations. Sufficient data is not available in the population PK analysis to guide the dose adjustment in patients with moderate to severe renal impairment or end stage renal disease ($CL_{CR} \geq 15$ mL/min to <60 mL/min) and patients with hepatic impairment.

4.4.3 Exposure-Response Analysis for Efficacy

The Applicant conducted exposure-response (E-R) analyses separately for T1DM and T2DM to quantify the relationship between insulin lispro concentration and postprandial glucose response following SC administration of LYUMJEV and Humalog® when both insulins are given prior to the start of the meal and 20 minutes after the start of the meal.

Data

A total of 1469 glucose concentrations for LYUMJEV and 1489 glucose concentrations for Humalog from Trial ITRV were included for the development of E-R model in patients with T1DM, while a total of 1482 glucose concentrations and 556 C-peptide concentrations for LYUMJEV and 1462 glucose concentrations and 540 C-peptide concentrations for Humalog from Trial ITRW were included for the development of E-R model in patients with T2DM. A total of 8296 glucose concentrations (3047 for LYUMJEV pre-meal, 2236 for LYUMJEV post-meal and 3013 for Humalog pre-meal) collected from 1054 patients with T1DM during the MMTT at Visit 18 in Trial ITRM and a total of 9709 glucose concentrations (4870 for LYUMJEV and 4839 for Humalog) collected from 610 patients with T2DM during the MMTT at Visits 8 and 18 in Trial ITRN were used to evaluate the predictive performance of the IGI models.

Methods

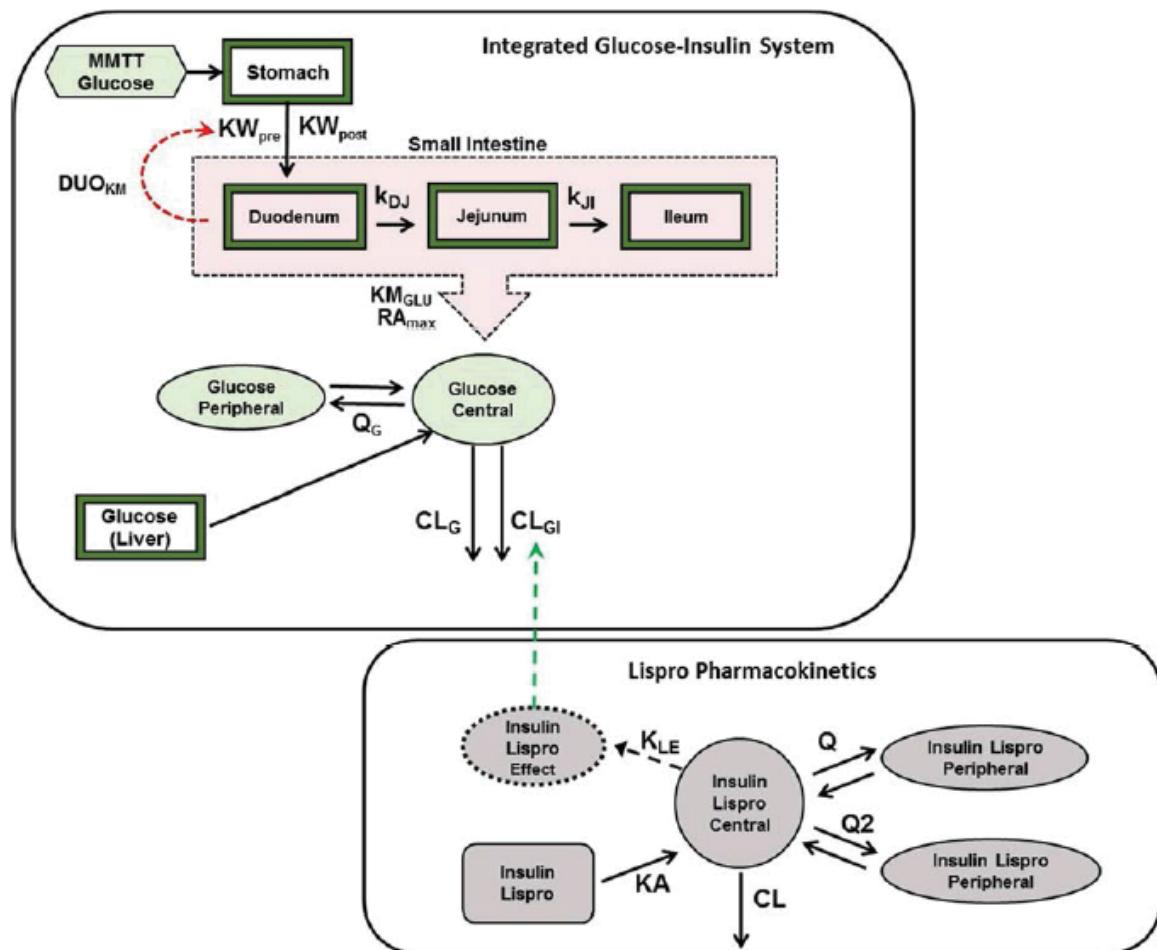
A sequential PK/PD modeling approach was used to analyze the E-R relationships among LYUMJEV or Humalog administration, serum insulin concentrations, and the corresponding effect on glucose concentrations. The individual PK parameters from the final insulin lispro PK model were merged with the NONMEM data set to predict the time course of insulin concentrations. The E-R relationships were described by an IGI model, a mechanistic model for characterizing the mechanistic feedback relationship between insulin and glucose which has been adapted to support the understanding of the effect of diabetes drugs, including insulin. Change in glucose profiles following a MMTT in Study ITRV and Study ITRW were characterized separately. To assess the predictive performance of the developed IGI models, glucose time courses following MMTT after 26 weeks of treatment were simulated in virtual patients and compared with the observed values in phase 3 trials ITRM and ITRN. Virtual patients were created by randomly selecting the baseline body weight, baseline blood glucose concentration and insulin lispro dose (LYUMJEV or Humalog), with replacement, from the distribution of each treatment arm in these two Phase 3 trials.

Results

IGI model for T1DM

The base structure of the IGI model for T1DM is shown in [Figure 36](#). The IGI model for T1DM includes: 1) a three-compartment model of insulin lispro, 2) a two-compartment model for glucose with transit absorption compartments, 3) the stimulatory effect of insulin on glucose elimination, 5) the inhibitory effect of glucose and insulin on hepatic glucose production. The majority of the parameters were fixed to the published values, while the following parameters, gastric emptying rate for premeal dosing (KW_{pre}), gastric emptying rate for postmeal dosing (KW_{post}), amount of glucose giving 50% of inhibition (DUO_{KM}), shape parameter for glucose inhibition of gastric emptying (GAMMA), amount of glucose giving 50% of maximum absorption (KM_{GLU}), amount of insulin giving 50% of maximum inhibition of glucose production (EC_{50}), and shape parameter for insulin inhibition of glucose production (HILL) parameters values were estimated simultaneously, as well as the IIV for DUO_{KM} and the residual variability. The parameter estimates and the corresponding estimates of precision (95% CI) from Bootstrap for the optimized IGI model for patients with T2DM based on data from Trial ITRM is provided in [Table 24](#).

Figure 36 Base Structure of the IGI Model for T1DM



Abbreviations: CL = insulin lispro clearance; CL_G = insulin independent glucose clearance; CL_{GI} = endogenous insulin dependent glucose clearance; DUO_{KM} = amount of glucose in duodenum giving 50% of maximum inhibition of gastric emptying; KA = insulin lispro first-order absorption rate constant; k_{DJ} = rate constant for glucose movement from duodenum to jejunum; k_{JI} = rate constant for glucose movement from jejunum to ileum; k_{LE} = rate constant for insulin lispro effect compartment related to CL_{GI} ; KM_{GLU} = amount of glucose giving 50% of maximum absorption; KW_{pre} = gastric emptying rate for premeal dosing; KW_{post} = gastric emptying rate for meal for post meal dosing; MMTT = mixed meal tolerance test; Q = intercompartmental clearance between insulin lispro central compartment and peripheral compartment 1; Q_2 = intercompartmental clearance between insulin lispro central compartment and peripheral compartment 2; RA_{max} = maximum rate of absorption from small intestine.

(Source: Applicant's Population PK/PD Report Figure 8.15.)

Table 24 Parameter Estimates of the Optimized Integrated Glucose Insulin Model for T1DM

Model		Optimized			
Parameter		Estimate (%RSE)	IIV (%CV)	Bootstrap Median (95%CI)	Bootstrap IIV (%CV)
Gastric emptying					
Emptying rate pre-dose (/min) (KW_{pre})	Θ_{19}	0.0458 <i>fix^g</i>	135 <i>fix^g</i>	0.0458 <i>fix^g</i>	135 <i>fix^g</i>
Emptying rate post-dose (/min) (KW_{post})	Θ_{20}	0.167 <i>fix^g</i>	135 <i>fix^g</i>	0.167 <i>fix^g</i>	135 <i>fix^g</i>
Amount of glucose giving 50% of inhibition (cg) (DUO_{50})	Θ_2	474 (13.3)	73.3 (10.2)	492 (326, 674)	66.4 (19.9, 134)
Shape parameter for glucose inhibition (GAMMA)	Θ_3	14 <i>fix^a</i>	7.1 <i>fix^f</i>	14 <i>fix^a</i>	7.1 <i>fix^f</i>
Delay in emptying for the meal (min)	Θ_8	0.0368 <i>fix^e</i>	7.1 <i>fix^f</i>	0.0368 <i>fix^e</i>	7.1 <i>fix^f</i>
Glucose absorption					
Maximum rate of absorption from duodenum (cg/h)	Θ_{13}	3480 <i>fix^a</i>	7.1 <i>fix^f</i>	3480 <i>fix^a</i>	7.1 <i>fix^f</i>
Maximum rate of absorption from jejunum (cg/h)	Θ_{14}	12400 <i>fix^a</i>	7.1 <i>fix^f</i>	12400 <i>fix^a</i>	7.1 <i>fix^f</i>
Maximum rate of absorption from ileum (cg/h)	Θ_{15}	7980 <i>fix^a</i>	7.1 <i>fix^f</i>	7980 <i>fix^a</i>	7.1 <i>fix^f</i>
Amount of glucose giving 50% of maximum absorption (cg) (KM_{GLU})	Θ_{12}	2290 (8.7)	7.1 <i>fix^f</i>	2320 (1490, 4130)	7.1 <i>fix^f</i>
First pass effect on glucose	Θ_1	0.80 <i>fix^b</i>	7.1 <i>fix^f</i>	0.80 <i>fix^b</i>	7.1 <i>fix^f</i>
Glucose disposition					
Insulin-independent glucose clearance (L/h)	Θ_4	1.89 <i>fix^e</i>	59.3 <i>fix^d</i>	1.89 <i>fix^e</i>	59.3 <i>fix^d</i>
Maximum insulin-dependent glucose clearance (L/h)	Θ_5	21.8 <i>fix^e</i>	54.0 <i>fix^e</i>	21.8 <i>fix^e</i>	54.0 <i>fix^e</i>
Central volume of distribution (L)	Θ_6	9.33 <i>fix^c</i>	7.1 <i>fix^f</i>	9.33 <i>fix^c</i>	7.1 <i>fix^f</i>
Peripheral volume of distribution (L)	Θ_7	8.56 <i>fix^c</i>	7.1 <i>fix^f</i>	8.56 <i>fix^c</i>	7.1 <i>fix^f</i>
Intercompartmental clearance (L/h)	Θ_9	26.5 <i>fix^c</i>	7.1 <i>fix^f</i>	26.5 <i>fix^c</i>	7.1 <i>fix^f</i>
Rate constant for glucose effect compartment (/h) (K_{LE})	Θ_{10}	2.1 <i>fix^e</i>	7.1 <i>fix^f</i>	2.1 <i>fix^e</i>	7.1 <i>fix^f</i>
Formation of endogenous glucose during the meal period (mg)	Θ_{16}	4.79 (14)	7.1 <i>fix^f</i>	5.54 (4.33, 7.51)	7.1 <i>fix^f</i>
Concentration of insulin lispro giving 50% of maximum insulin-dependent glucose clearance (pmol/mL)	Θ_{17}	338 (9.4)	7.1 <i>fix^f</i>	329 (253, 497)	7.1 <i>fix^f</i>
Shape parameter for insulin lispro	Θ_{18}	1.86 (10.4)	7.1 <i>fix^f</i>	1.9 (1.37, 2.36)	7.1 <i>fix^f</i>
Residual variability (%)	Θ_{11}	22.2 (1.4)		21.9 (18.3, 25.0)	

Abbreviations: %RSE = relative standard error of the estimate as a percentage; CI = confidence interval; T1DM = type 1 diabetes mellitus.

a Fixed to value from Alskär et al. 2016.

b Fixed to value from Hovorka et al. 2004.

c Fixed to value from Silber et al. 2010.

d Fixed to value from Schneck et al. 2013.

e Fixed to value from CSII model (Lilly data on file).

f Fixed to facilitate efficient operation of the SAEM algorithm.

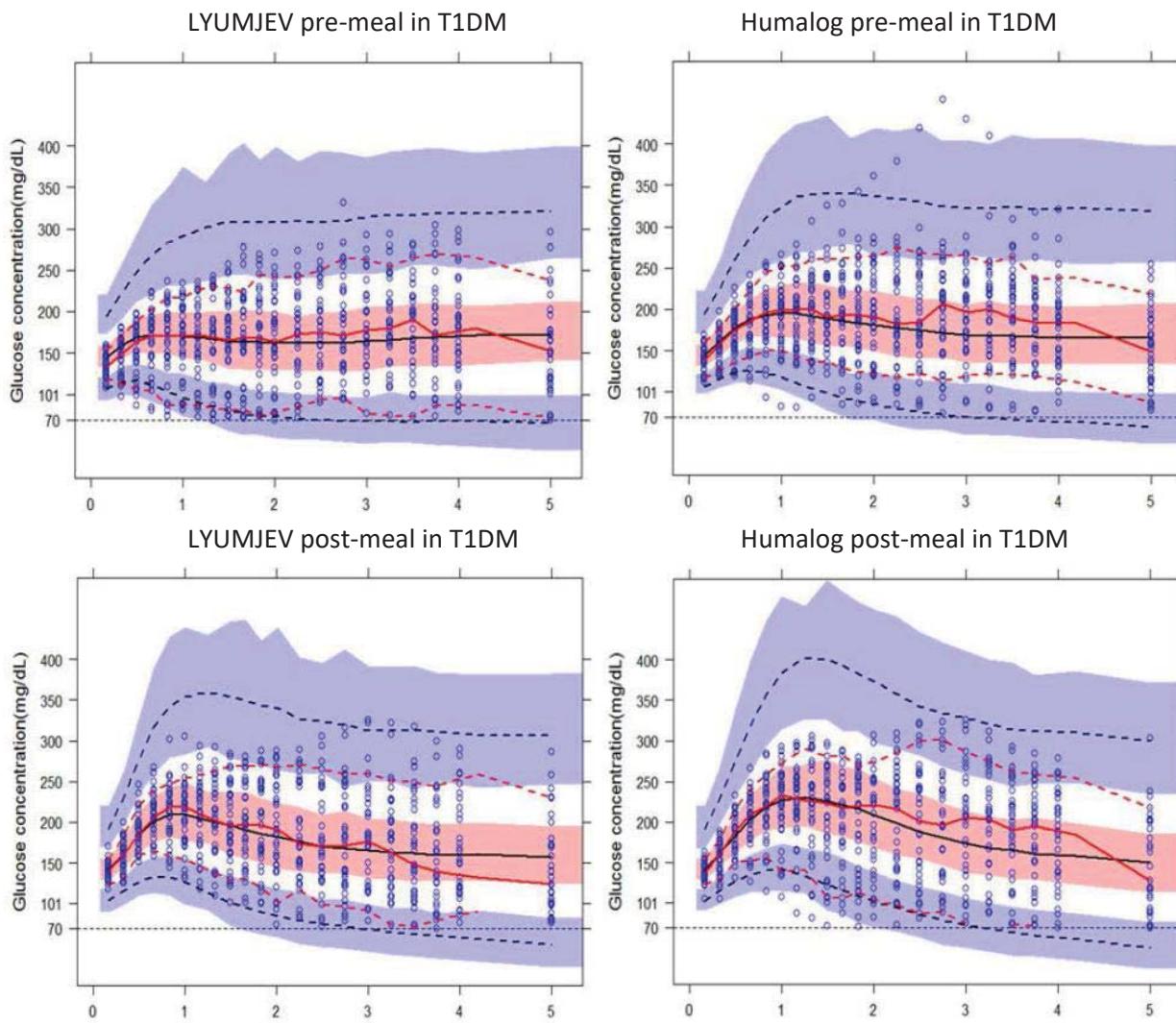
g Fixed to value from sensitivity analysis.

(Source: Applicant's Population PK/PD Report Table 8.6.)

The VPCs for the modified IGI model in patients with T1DM stratified by treatment (LYUMJEV or Humalog) and administration time (pre-meal administration or 20 minutes post-meal administration) showed that the modified IGI model was generally able to correctly predict glucose dynamic data (Figure 37).

The glucodynamic parameter estimates were not found to have overt relationships with age, sex, duration of diabetes, insulin lispro dose amount, glargine dose amount, and total daily insulin dose amount. Due to the limited study size (35 subjects for LYUMJEV and 36 subjects for Humalog), insufficient data were available for robust assessment of the impacts of race or ethnicity, concomitant oral antihyperglycemics, or baseline HbA1c on the parameter estimates. The impact of baseline fasting plasma glucose on the glucodynamic parameters was not assessed since the observed glucose at the start of MTT may not reflect steady-state conditions.

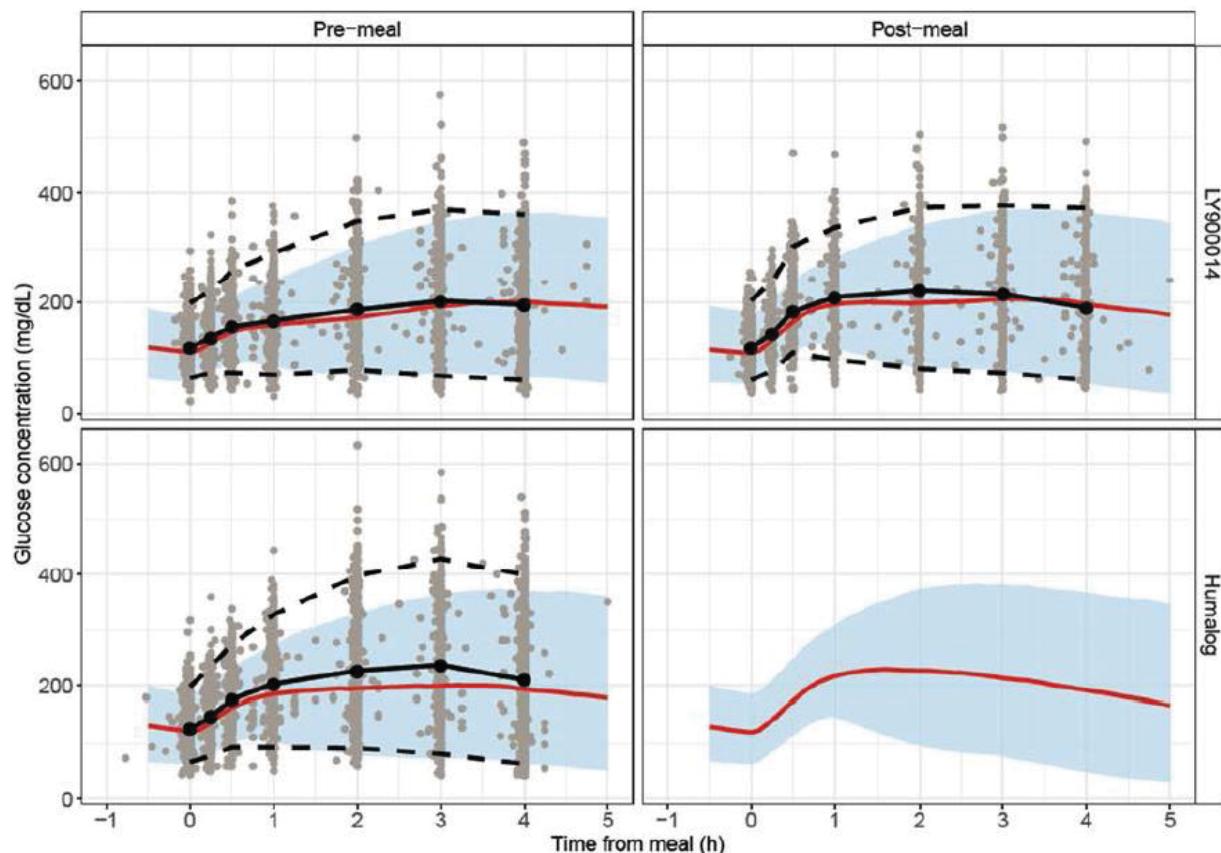
Figure 37 Visual Predictive Check of the Model Predictions of Glucose Concentration during the Breakfast MMTT following Administration of LYUMJEV or Humalog Immediately Prior to the Start of the Meal or 20 Minutes Post Meal in Patients with T1DM



(Source: Applicant's Population PK/PD Report Figures 8.20, 8.21, 8.22 and 8.23.)

The model-predicted glucose time courses following MMTT after 26 weeks of pre-meal or post-meal treatment of LYUMJEV or Humalog for patients with T1DM were plotted in Figure 38 against the observed glucose data in Trial ITRM. The Applicant stated that there was good agreement between the median of the observed and median of the simulated glucose concentrations. The 5% prediction interval (PI) was well described, but the 95% PI tended to be slightly underpredicted except at the 4-hour time point. In general, it appeared that the IGI model predicted a better glucose lowering effect for Humalog than observed at 2- and 3-hour post-dose in Trial ITRM. The simulations also indicated that LYUMJEV would have better post-prandial glucose lowering compared to Humalog when both insulins are administered 20 minutes after the start of the meal.

Figure 38 Comparison of Observed Glucose vs. Model-predicted Glucose Time Course following MMTT after 26 Weeks of Treatment for Patients with T1DM Randomized to either LYUMJEV or Humalog when Given Immediately before the Meal or 20 Minutes after the Start of the Meal in Study ITRM.



Note: Gray circles represent observed glucose concentrations from Phase 3 Study ITRM. Black circles and black solid line represent median of observed glucose concentrations. Black dashed lines represent the 5th and 95th percentiles of observed glucose concentrations. The solid red line represents the median of the simulation based on the T1DM IGI model and the shaded area denotes the 90% PI.

Abbreviations: IGI = integrated glucose-insulin; PI = prediction interval; T1DM = type 1 diabetes mellitus.

(Source: Applicant's Population PK/PD Report Figure 10.3.)

The Applicant conducted simulations to predict the postprandial glucose (PPG) excursion at 1 and 2 hours from 300 virtual patients, which were randomly selected with the baseline body weight, baseline blood glucose concentration, and individualized insulin lispro dose from the distribution of each treatment arm on visit 18 in Trial ITRM. The model predicted mean difference and 95% CI based on 10,000 replicates between LYUMJEV and Humalog for the PPG excursion at 1 and 2 hours when both insulins are given immediately before the start of the meal were comparable to the data from Trial ITRM (Table 25). The Applicant concluded that LYUMJEV has a significantly greater glucose lowering effect than Humalog when LYUMJEV and Humalog are given prior to start of meal or 20 minutes after the start of the meal.

Table 25 Comparison of Observed and Model Predicted Glucose Excursions Difference between LYUMJEV and Humalog in Patients with T1DM

	Units	Pre-meal (All data)	Pre-meal (w/ Exclusion)	Pre-meal	Post-meal
		Observed ITRM LSM Difference (95% CI)	Observed ITRM Mean Difference (95% CI)	Model Predicted Mean Difference ^b (95%CI)	Model Predicted Mean Difference ^b (95%CI)
PPG Excursion at 1h [LY900014 relative to Humalog]	mg/dL	-27.9 ^a (-35.3, -20.6)	-25.2 (-33.1, -17.2)	-24.0 (-32.2, -16.0)	-22.2 (-30.1, -14.3)
	mmol/L	-1.55 ^a (-1.96, -1.14)	-1.40 (-1.84, -0.955)	-1.33 (-1.79, -0.888)	-1.23 (-1.67, -0.794)
PPG Excursion at 2h [LY900014 relative to Humalog]	mg/dL	-31.2 ^a (-41.1, -21.2)	-25.7 (-37.1, -14.3)	-19.6 (-30.7, -8.54)	-23.7 (-35.6, -11.9)
	mmol/L	-1.73 ^a (-2.28, -1.18)	-1.43 (-2.06, -0.794)	-1.09 (-1.70, -0.474)	-1.32 (-1.98, -0.660)

Abbreviations: Pre-meal = administered immediately (0-2 minutes) prior to the start of the meal; Post-meal = administered 20 minutes after start of meal; LSM = least squares mean; CI = confidence interval; PPG = postprandial glucose.

^a p <0.001.

^b Based on a bootstrap analysis of model predicted glucose, consisting of 10,000 replicates of the mean of 300 sampled glucose excursion for LY900014 or Humalog and the calculated difference of the means. The arithmetic mean and 2.5th and 97.5th percentiles of the 10,000 replicates are shown.

(Source: Applicant's Population PK/PD Report Table 10.3.)

The Applicant also predicted PPG excursion at 1 and 2 hours between LYUMJEV and Humalog when Humalog is administered immediately before the start of the meal (pre-meal) to when LYUMJEV is administered 20 minutes after the start of the meal (post-meal), which was believed compared to the observed data in Trial ITRM (Table 26). The Applicant stated that the predicted mean difference and 95% CI between LYUMJEV and Humalog for the PPG excursion at 1 and 2 hours were similar to the observed data.

Table 26 Comparison of Observed and Model Predicted Glucose Excursions Difference between LYUMJEV and Humalog when LYUMJEV is Given 20 Minutes after the Start of Meal to when Humalog is Given Immediately before the Start of the Meal in Patients with T1DM

	Units	Observed ITRM Mean Difference (95% CI)	Model Predicted Mean Difference ^a (95%CI)
PPG Excursion at 1h [LY900014 post-meal relative to Humalog pre-meal]	mg/dL	16.9 (8.78, 25.0)	12.8 (4.68, 20.9)
	mmol/L	0.938 (0.487, 1.39)	0.710 (0.260, 1.16)
PPG Excursion at 2h [LY900014 post-meal relative to Humalog pre-meal]	mg/dL	-1.91 (-13.5, 9.52)	6.27 (-5.33, 17.8)
	mmol/L	-0.106 (-0.749, 0.528)	0.348 (-0.296, 0.988)

Abbreviations: Pre-meal = administered immediately prior (0-2 minutes) to start of meal; Post-meal = administered 20 minutes after start of meal; LSM = least squares mean; CI = confidence interval; PPG = postprandial glucose.

^a Based on a bootstrap analysis of model predicted glucose, consisting of 10,000 replicates of the mean of 300 sampled glucose excursion for LY900014 or Humalog and the calculated difference of the means. The arithmetic mean and 2.5th and 97.5th percentiles of the 10,000 replicates are shown.

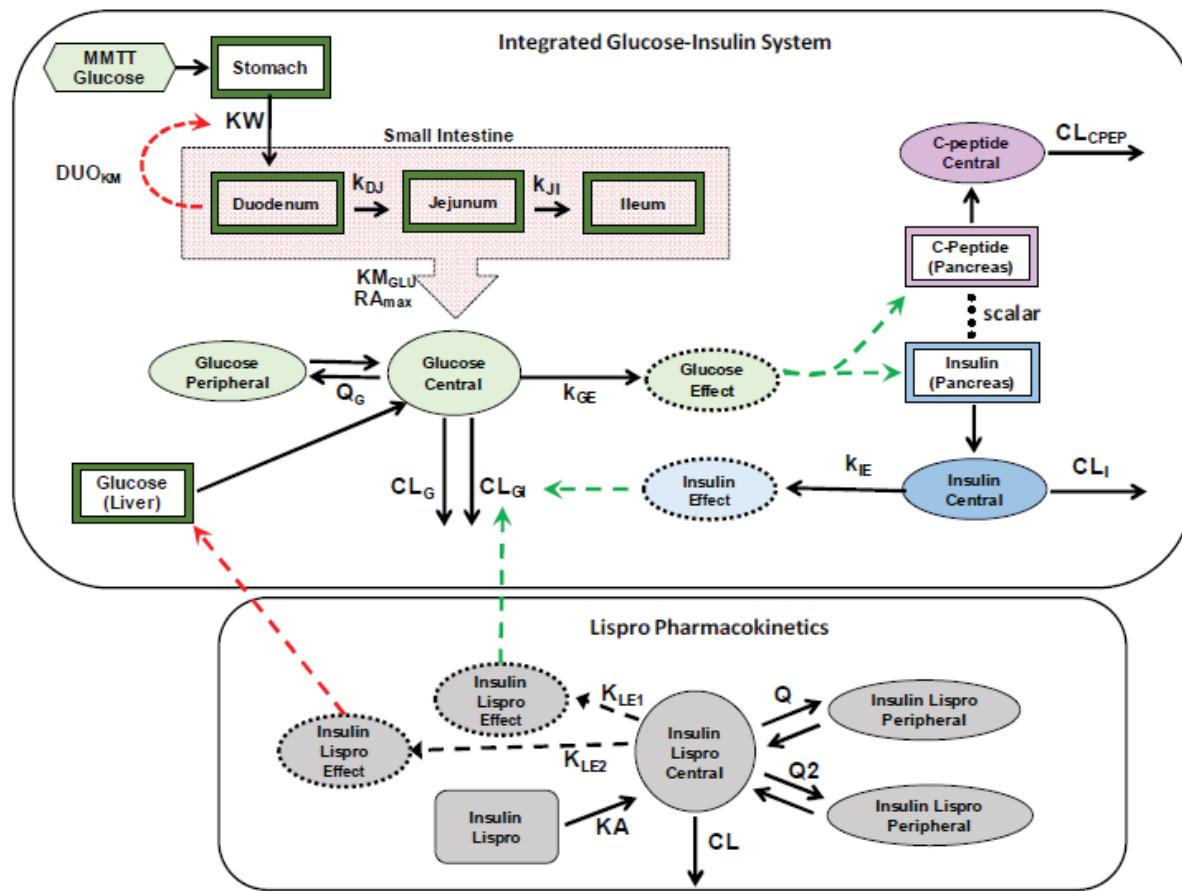
(Source: Applicant's Population PK/PD Report Table 10.4.)

IGI model for T2DM

The Applicant adapted an IGI structure model (Figure 39) predominantly from publications to characterize glucose time profiles in patients with T2DM following administration of LYUMJEV or Humalog in Trial ITRW. The IGI model for T2DM includes: 1) a three-compartment model of insulin lispro, 2) a two-compartment model for glucose with transit absorption compartments, 3) a one-compartment model for c-peptide, 4) a one-compartment model for endogenous insulin, 5) the stimulatory

effect of glucose on endogenous insulin production and c-peptide, 6) the stimulatory effect of both endogenous and administered insulin on glucose elimination, and 7) the inhibitory effect of glucose and insulin on hepatic glucose production. Per literature, endogenous insulin concentrations were assumed a fraction of plasma C-peptide concentrations due to hepatic extraction of endogenous insulin following secretion of equivalent molar amounts of endogenous insulin and C-peptide from the pancreas. The stimulatory effect of glucose on C-peptide secretion was assumed to have the same magnitude impact on endogenous insulin secretion.

Figure 39 Schematic Representation of the Insulin Lispro PK Model Linked to the Adapted IGI Model for Patients with T2DM.



Abbreviations: MMTT=mixed meal tolerance test; KM_{GLU} = amount of glucose giving 50% of maximum absorption; RA_{max} = maximum rate of absorption from small intestine; KW = gastric emptying rate; DUO_{KM} = amount of glucose in duodenum giving 50% of maximum inhibition of gastric emptying; k_{DJ} = rate constant for glucose movement from duodenum to jejunum; k_{JI} = rate constant for glucose movement from jejunum to ileum; Q_G = intercompartmental clearance between glucose central and glucose peripheral compartments; k_{GE} = rate constant for glucose effect compartment; CL_G = insulin-independent glucose clearance; CL_{GI} = insulin dependent glucose clearance; CL_{CPEP} = c-peptide clearance; k_{IE} = rate constant for endogenous insulin effect compartment; CL_I = endogenous insulin clearance; KA = insulin lispro absorption rate; K_{LE1} = rate constant for insulin lispro effect compartment related to CL_G ; K_{LE2} = rate constant for insulin lispro effect compartment related to hepatic glucose production; Q = clearance between insulin lispro central compartment and peripheral compartment 1; Q2 = clearance between insulin lispro central compartment and peripheral compartment 2; CL = insulin lispro clearance.

(Source: Applicant's Population PK/PD Report Figure 8.26.)

The insulin lispro concentrations were predicted using the individual post-hoc estimates for Trial ITRW patients derived from the insulin lispro PK final model. Most of the dynamic parameters regarding glucose absorption, glucose disposition and insulin disposition were fixed to published values estimated for patients with T2DM. Parameters including KW, DUOKM, KM_{GLU}, stimulatory effect of insulin lispro on glucose clearance, inhibitory effect of insulin lispro concentration on endogenous glucose production, and those with a relationship to c-peptide were estimated for Trial ITRW data. The dynamic parameters and the corresponding estimates of precision (95% CI) from Bootstrap for the optimized IGI model for patients with T2DM based on data from Trial ITRW are shown in Table 27.

Table 27 Parameter Estimates of the Optimized Integrated Glucose Insulin Model for T2DM (Trial ITRW)

Parameter		Estimate (%RSE)	IIV %CV	Bootstrap Median (95%CI)	Bootstrap IIV %CV (95% CI)
Gastric emptying					
Emptying rate (1/min) (KW)	Θ_{28}	0.00886 (19)	50.0 fix ^a	0.00545 (0.00173 – 0.0132)	50.0 fix ^a
Amount of glucose in duodenum giving 50% of inhibition (cg) (DUOKM)	Θ_{22}	557 (9.4)	32.9 fix ^f	581 (447 – 1130)	32.9 fix ^f
Shape parameter for intestinal glucose inhibition of gastric emptying	Θ_{23}	14 fix ^a	5.0 fix ^f	14 fix ^a	5.0 fix ^f
Delay in emptying for the meal (min)	Θ_7	0 fix ^b	0 fix ^b	0 fix ^b	0 fix ^b
Glucose absorption					
Maximum rate of absorption from duodenum (cg/h)	Θ_{19}	3480 fix ^a	21.0 fix ^f	3480 fix ^a	21.0 fix ^f
Maximum rate of absorption from jejunum (cg/h)	Θ_{20}	12400 fix ^a	24.0 fix ^f	12400 fix ^a	24.0 fix ^f
Maximum rate of absorption from ileum (cg/h)	Θ_{21}	7980 fix ^a	52.0 fix ^f	7980 fix ^a	52.0 fix ^f
Amount of glucose giving 50% of maximum absorption (cg) (KM _{GLU})	Θ_4	1760 (6.1)	32.4 fix ^f	2150 (1100 – 9660)	32.4 fix ^f
First pass effect on glucose	--	1 fix ^{a,b}	0 fix ^b	1 fix ^{a,b}	0 fix ^b
Glucose disposition					
Mean glucose concentration at meal start (mg/dL)	--	136 ^c	5.3 ^c	--	--
Insulin-independent glucose clearance (L/h) (CL _G)	Θ_5	1.72 fix ^d	59.1 fix ^d	1.72 fix ^d	59.1 fix ^d
Endogenous insulin-dependent glucose clearance (L/h)/(pmol/L) (CL _{GE})	Θ_{16}	0.0743 fix ^d	48.3 fix ^d	0.0743 fix ^d	48.3 fix ^d
Central volume of distribution (L) (V _G)	Θ_1	9.33 fix ^{d,e}	30.1 fix ^d	9.33 fix ^{d,e}	30.1 fix ^d
Peripheral volume of distribution (L) (V _P)	Θ_6	8.56 fix ^d	30.1 fix ^d	8.56 fix ^d	30.1 fix ^d
Intercompartmental clearance (L/h) (Q _G)	Θ_2	26.5 fix ^d	85.1 fix ^d	26.5 fix ^d	85.1 fix ^d
Rate constant for glucose effect compartment (1/h) (k _{GE})	Θ_{18}	0.738 fix ^d	53.1 fix ^d	0.738 fix ^d	53.1 fix ^d
Steady-state glucose concentration (mg/dL) (GSS)	Θ_8	156 (8.4)	32.1	153 (132 – 178)	32.1 (17.7 – 42.5)
Maximum glucose clearance dependent on insulin lispro (L/h)	Θ_{12}	0.0629 (9.5)	32.4 fix ^f	0.0332 (0.00943 – 0.161)	32.4 fix ^f

Parameter		Estimate (%RSE)	IIV %CV	Bootstrap Median (95%CI)	Bootstrap IIV %CV (95% CI)
Glucose disposition (continued)					
Concentration of insulin lispro giving 50% of maximum glucose clearance dependent on insulin lispro (pmol/L)	Θ_{11}	64.1 (3.2)	15.1 fix ^f	50.0 (19.5 – 94.4)	15.1 fix ^f
Shape parameter for insulin lispro relationship with glucose clearance	Θ_{10}	1.25 (1.4)	5.0 fix ^f	1.41 (1.05 – 1.73)	5.0 fix ^f
Rate constant for insulin lispro effect compartment on glucose clearance (1/h) (K_{LE1})	Θ_9	0.815 (1.9)	5.0 fix ^f	0.566 (0.392 – 0.832)	5.0 fix ^f
Concentration of insulin lispro giving 50% of maximum inhibition of EGP (pmol/L)	Θ_{31}	51.9 (2.1)	15.1 fix ^f	46.2 (27.9 – 77.9)	15.1 fix ^f
Shape parameter for insulin lispro inhibition of EGP	Θ_{30}	2.20 (0.6)	5.0 fix ^f	2.78 (2.05 – 3.87)	5.0 fix ^f
Rate constant for insulin lispro effect compartment on EGP (1/h) (K_{LE2})	Θ_{29}	0.507 (1.4)	5.0 fix ^f	0.464 (0.330 – 0.834)	5.0 fix ^f
Glucose residual variability (%)	Θ_{32}	13.7 (1.0)	--	13.4 (12.1 – 14.8)	--
C-peptide disposition					
Mean c-peptide concentration at meal start (pmol/L)	--	508 ^c	41.8 ^c	--	--
Volume of distribution (mL) (V_{CP})	Θ_{25}	69.3 ^e (7.5)	32.4 fix ^f	48.2 (13.5 – 234)	32.4 fix ^f
Clearance (L/h) (CL_{CP})	Θ_{26}	102 (4.3)	32.4 fix ^f	63.0 (8.65 – 200)	32.4 fix ^f
Steady-state c-peptide concentration (pmol/L)	Θ_{27}	898 (12.9)	121.6	870 (598 – 1200)	116 (66.0 – 215)
Fractional scalar of baseline c-peptide relative to baseline insulin	Θ_{24}	0.373 (5.3)	15.9 fix ^f	0.247 (0.0419 – 0.439)	15.9 fix ^f
C-peptide residual variability (%)	Θ_{33}	22.8 (1.7)	--	22.5 (19.0 – 26.0)	--
Endogenous insulin disposition					
Steady-state insulin concentration (pmol/L) (ISS)	Θ_{13}	113 (10.6)	49.1 fix ^d	102 (75.4 – 135)	49.1 fix ^d
Volume of distribution (L) (V_I)	Θ_3	6.09 fix ^{d,e}	41.1 fix ^d	6.09 fix ^{d,e}	41.1 fix ^d
Clearance (L/h) (CL_I)	Θ_{14}	73.2 fix ^d	29.0 fix ^d	73.2 fix ^d	29.0 fix ^d
Rate constant for endogenous insulin effect compartment on CL_{GI} (1/h) (k_{IE})	Θ_{17}	0.464 fix ^d	44.9 fix ^d	0.464 fix ^d	44.9 fix ^d
Control parameter for the glucose effect on endogenous insulin secretion (IPRG)	Θ_{15}	1.91 (5.7)	35.1 fix ^d	1.96 (1.62 – 2.36)	35.1 fix ^d
Parameter Correlation					
Corr V_G - Q_G	--	-0.75 fix ^d	--	--	--
Corr V_G - V_I	--	0.71 fix ^d	--	--	--
Corr Q_G - V_I	--	-0.35 fix ^d	--	--	--

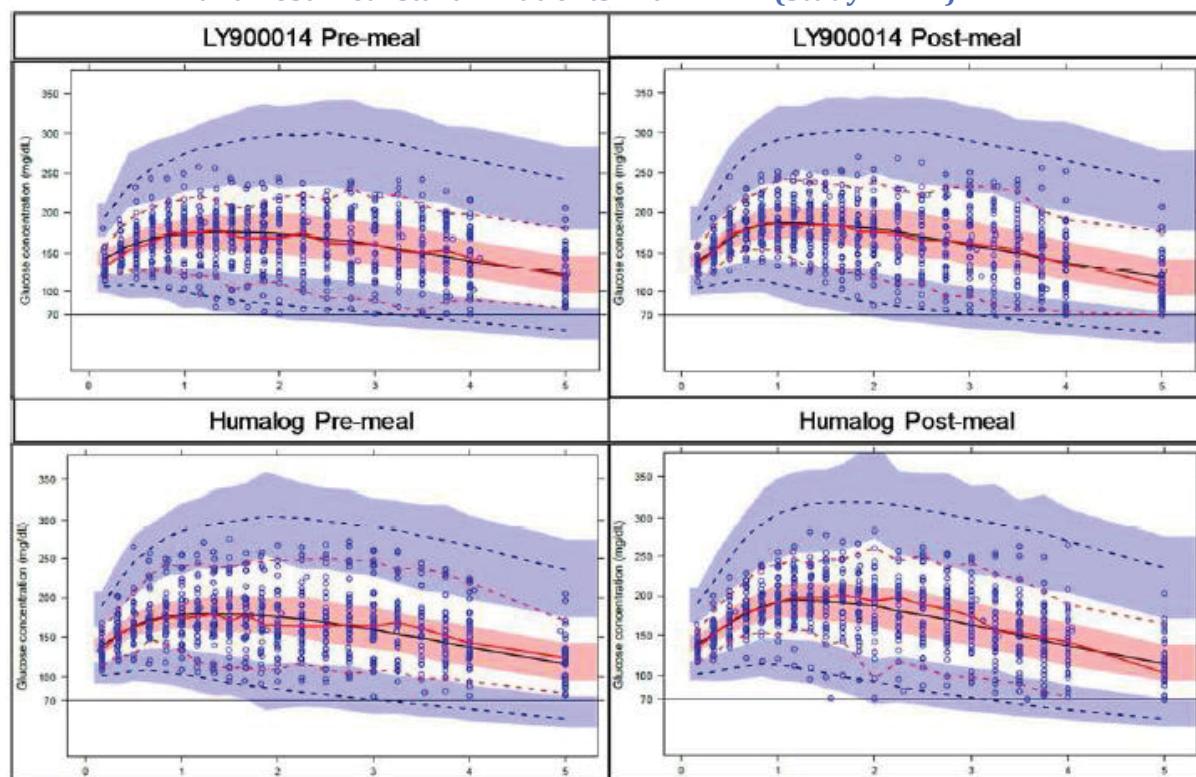
Abbreviations: %RSE = relative standard error of the estimate as a percentage; IIV = inter-individual variability; %CV = coefficient of variation as a percentage; cg = centigram ($\text{cg/L} = \text{mg/dL}$); CI = confidence interval; EGP = endogenous glucose production; Corr = correlation; T2DM = type 2 diabetes mellitus.

- a Fixed to value from Alskär et al. 2016.
- b Fixed to value after estimation caused model performance issues (eg. model instability, unreliable parameter estimate, parameter estimate deemed to have minimal impact on model fit).
- c Reported as mean and %CV of observations.
- d Fixed to value from Jauslin et al. 2011.
- e Reported for 70 kg individual. Model incorporated allometric scaling: $V_d = \Theta \times \text{WT}/70$, where V_d is the volume of distribution of an individual, Θ is the population parameter estimate, and WT is the body weight (kg) of an individual. Study ITRW median baseline body weight = 96.9 kg.
- f Fixed to value deemed reasonable to facilitate efficient operation of the SAEM algorithm and based on information reported in Jauslin et al 2011.

(Source: Applicant's Population PK/PD Report Table 8.7.)

VPCs of glucose (Figure 40) and C-peptide (Figure 41) time profiles for the optimized IGI model in patients with T2DM following LYUMJEV or Humalog administered pre-meal start or 20 minutes post-meal start showed apparent fidelity between observations and predictions.

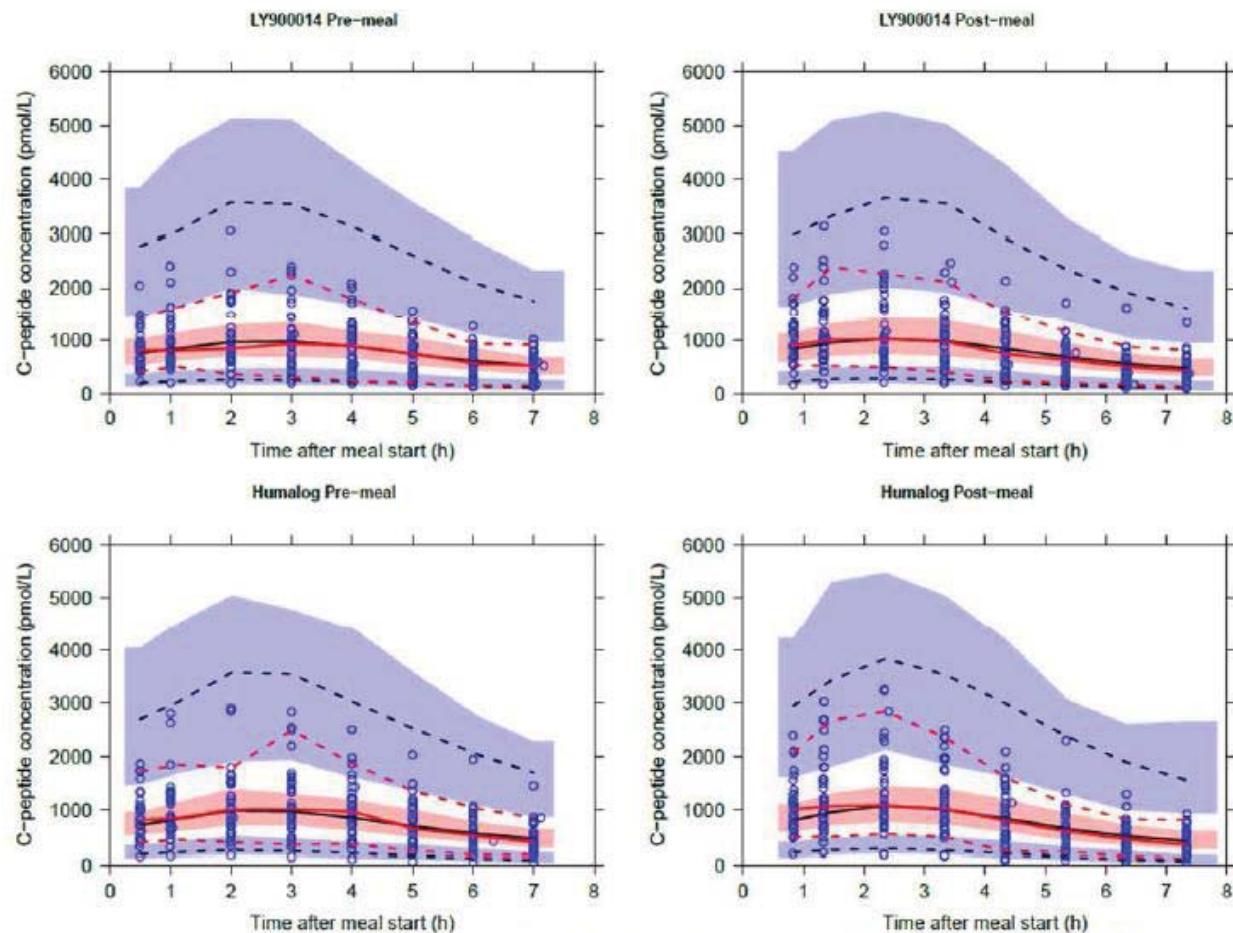
Figure 40 Visual Predictive Check of the Optimized Model Predictions of Glucose Concentrations following LYUMJEV and Humalog Administered Pre-meal Start and Post-meal start in Patients with T2DM (Study ITRW).



Note: The blue circles represent observed data. The solid red line depicts median observed data and the red dashed lines represent the 5th and 95th percentiles of data. The pink shaded area defines 95% confidence interval around the median of the simulated data and the blue shaded areas represent simulated 95% confidence intervals around the 5th and 95th percentiles of the simulated data. The solid black line represents the median of the prediction interval and the black dashed lines represent the lower and upper bounds of the 90% prediction interval.

(Source: Applicant's Population PK/PD Report Figure 8.31.)

Figure 41 Visual Predictive Check of the Optimized Model Predictions of C-peptide Concentrations following LYUMJEV and Humalog Administered Pre-meal Start and Post-meal start in Patients with T2DM (Study ITRW).

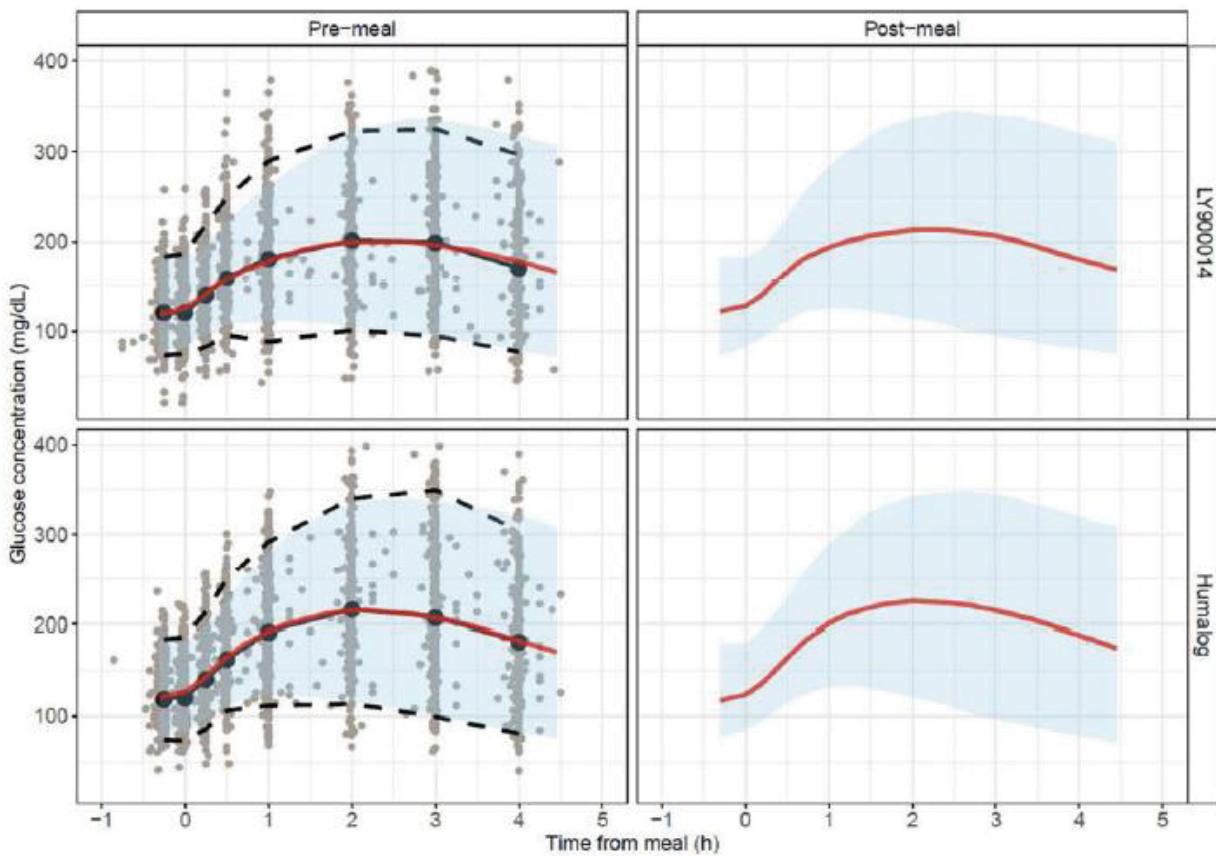


Note: The blue circles represent observed data. The solid red line depicts median observed data and the red dashed lines represent the 5th and 95th percentiles of data. The pink shaded area defines the 95% confidence interval around the median of the simulated data and the blue shaded areas represent simulated 95% confidence intervals around the 5th and 95th percentiles of the simulated data. The solid black line represents the median of the prediction interval and the black dashed lines represent the lower and upper bounds of the 90% prediction interval.

(Source: Applicant's Population PK/PD Report Figure 8.30.)

The Applicant stated that steady-state endogenous insulin concentration (ISS) and endogenous insulin dependent glucose clearance (CL_{GI}) in the IGI model may reflect insulin sensitivity. Changes in ISS may represent changes in beta-cell secretory capacity, such that a lower ISS may signify decreased pancreatic insulin secretion. The CL_{GI} parameter value may be lower when insulin resistance is higher. When ISS was decreased by 20% and CL_{GI} was decreased by 30%, the model predicted glucose time courses in patients with T2DM following MMTT after 26 weeks of pre-meal or post-meal treatment of LYUMJEV or Humalog showed fidelity with the observed glucose from ITRN (Figure 42).

Figure 42 Comparison of Observed Glucose vs. Model-predicted Glucose Time Course following MMTT after 26 Weeks of Treatment for Patients with T2DM Randomized to either LYUMJEV or Humalog when Given Immediately before the Meal or 20 Minutes after the Start of the Meal in Study ITRN.



Note: Gray circles represent observed glucose concentrations from Phase 3 Study ITRN. Black circles and black solid line represent median of observed glucose concentrations. Black dashed lines represent the 5th and 95th percentiles of observed glucose concentrations. A simulation with the calibrated PKPD model for patients with T2DM in Study ITRN was conducted with 2000 replicates. The solid red line represents the median of the simulation and the shaded area denotes the 90% prediction interval.

Abbreviations: MMTT = mixed meal tolerance test; PKPD = pharmacokinetics/pharmacodynamics; T2DM = type 2 diabetes mellitus.

(Source: Applicant's Population PK/PD Report Figure 10.5.)

A bootstrap analysis was performed on the PPG at 1 hour and 2 hours using the pool of simulated 300 virtual patients receiving either LYUMJEV or Humalog for 10,000 times. The Applicant stated that the model predicted a similar mean difference and 95% CI between LYUMJEV and Humalog for the PPG excursion at 1 and 2 hours when both insulins are given immediately before the start of the meal, as observed in Trial ITRN (Table 28).

The Applicant also predicted PPG excursion at 1 and 2 hours between LYUMJEV and Humalog when Humalog is administered immediately before the start of the meal to when LYUMJEV is administered 20 minutes after the start of the meal (Table 29). The Applicant stated that the predicted mean and 95% CI between LYUMJEV and Humalog for the PPG excursion at 1 and 2 hours were not significantly

different, indicating a similar PPG excursion for when LYUMJEV is dosed 20 minutes post meal to when Humalog is dosed immediately before the start of the meal.

Table 28 Comparison of Observed and Model Predicted Glucose Excursions Difference between LYUMJEV and Humalog in Patients with T2DM

	Units	Pre-meal	Pre-meal	Post-meal
		Observed ITRN LS Mean Difference (95% CI)	Model Predicted Mean Difference b (95%CI)	Model Predicted Mean Difference b (95%CI)
PPG Excursion at 1h [LY900014 relative to Humalog]	mg/dL	-11.8 a (-18.1, -5.5)	-15.7 (-25.2, -6.1)	-10.1 (-19.9, -0.6)
	mmol/L	-0.66 a (-1.01, -0.30)	-0.87 (-1.40, -0.34)	-0.56 (-1.10, -0.03)
PPG Excursion at 2h [LY900014 relative to Humalog]	mg/dL	-17.4 a (-25.3, -9.5)	-15.3 (-28.3, -2.1)	-12.8 (-26.5, 0.7)
	mmol/L	-0.96 a (-1.41, -0.52)	-0.85 (-1.57, -0.11)	-0.71 (-1.47, 0.04)

Abbreviations: Pre-meal = administered immediately (0-2 minutes) prior to start of meal; Post-meal = administered 20 minutes after start of meal; LS = least squares; CI = confidence interval; PPG = postprandial glucose.

^a p <0.001

^b Based on a bootstrap analysis of model predicted glucose, consisting of 10,000 replicates of the mean of 300 sampled glucose excursion for LY900014 or Humalog and the calculated difference of the means. The arithmetic mean and 2.5th and 97.5th percentiles of the 10,000 replicates are shown.

(Source: Applicant's Population PK/PD Report Table 10.6.)

Table 29 Comparison of Observed and Model Predicted Glucose Excursions Difference between LYUMJEV and Humalog when LYUMJEV is Given 20 Minutes after the Start of Meal (Post-meal) to when Humalog is Given Immediately before the Start of the Meal (Pre-meal) in Patients with T2DM

	Units	Model Predicted Mean Difference a (95%CI)
PPG Excursion at 1h [LY900014 post-meal relative to Humalog pre-meal]	mg/dL	-1.7 (-11.3, 8.1)
	mmol/L	-0.10 (-0.63, 0.45)
PPG Excursion at 2h [LY900014 post-meal relative to Humalog pre-meal]	mg/dL	-3.2 (-16.5, 9.9)
	mmol/L	-0.18 (-0.91, 0.55)

Abbreviations: Pre-meal = administered immediately prior (0-2 minutes) to start of meal; Post-meal = administered 20 minutes after start of meal; CI = confidence interval; PPG = postprandial glucose.

^a Based on a bootstrap analysis of model predicted glucose, consisting of 10,000 replicates of the mean of 300 sampled glucose excursion for LY900014 or Humalog and the calculated difference of the means. The arithmetic mean and 2.5th and 97.5th percentiles of the 10,000 replicates are shown.

(Source: Applicant's Population PK/PD Report Table 10.7.)

Reviewer's Comments:

The Applicant's modified IGI model generally captured the mean trend of glucose dynamics following administration of LYUMJEV or Humalog prior to start or after the start of a MMTT in patients with T1DM in Phase 1 Trial ITRV. The IGI model predicted glucose concentrations at 2 and 3 hours were

slightly lower than the observed values in patients with T1DM following MMTT after 26 weeks of treatment Humalog when given immediately before the meal in Trial ITRM. In addition, the model predicted difference in PPG excursion at 2 hours was slightly higher than that observed in Trial ITRM for when LYUMJEV is dosed 20 minutes post meal to when Humalog is dosed immediately before the start of the meal. This is probably because: 1) the test meal was well controlled in Phase 1 Trial ITRV versus that uncontrolled in the Phase 3 Trial ITRM , 2) Trial ITRV was a single dose trial versus a long term duration for Trial ITRM, and 3) the lack of individual carbohydrate consumption and insulin PK data from Phase 3 trial ITRM limited the IGI model's capacity of producing accurate simulation for the incidences of all documented hypoglycemia in patients with T1DM.

The Applicant's modified IGI model appears adequate to describe the glucose dynamics following administration of LYUMJEV or Humalog prior to start or after the start of a MMTT in patients with T2DM in Phase 1 Trial ITRW. In addition, the model well predicted the lower postprandial glucose with LYUMJEV compared to Humalog as observed in Phase 3 Trial ITRN when both insulins were given prior to the start of a meal. The Applicant's simulation demonstrated a similar PPG excursion for when LYUMJEV is dosed 20 minutes post meal to when Humalog is dosed immediately before the start of the meal, which supports the proposed administration of LYUMJEV within 20 minutes after starting a meal in patients with T2DM from the efficacy perspective.

4.4.4 Exposure-Response Analysis for Safety

Per the Agency's request, the Applicant used the modified IGI models developed in patients with T1DM or T2DM to perform the simulations of the glucose response and tabulate incidence of hypoglycemia with BG \leq 70 mg/dL and BG $<$ 54 mg/dL at \leq 0.5, \leq 1, \leq 2, \leq 4, >1 to \leq 2, and >2 to \leq 4 hours for

- LYUMJEV administered immediately prior to each meal,
- Humalog administered immediately prior to each meal,
- LYUMJEV administered 20 minutes after the start of a meal, and
- Humalog administered 20 minutes after the start of a meal.

Data

The number of observed individual PPG values \leq 70 mg/dL or \leq 54 mg/dL during the MMTT at Week 26 in Phase 3 Trials ITRM and ITRN were used to compare to the model predicted rate and incidence of hypoglycemia.

Methods

A total of 1000-time simulations using 300 virtual patients reflective of the phase 3 patient populations (body weight, insulin dose, pre-meal glucose) were conducted using 100 g of carbohydrate, representative of 2 cans of Ensure (used for the MMTT in the Phase 3 studies), and were compared with the observed hypoglycemia data in Phase 3 Trials ITRM and ITRN for the MMTT at week 26. Additionally, simulations were conducted with lower amount of test meal carbohydrates (in order to simulate conditions in which hypoglycemia is more likely to occur) to assess the impact on the incidence of hypoglycemia in patients with T1DM and T2DM. The conditions for the simulations were the same in order to enable the comparison of LYUMJEV and Humalog.

Results

Simulations in T1DM

Summaries of the number of simulated BG \leq 70 mg/dL or BG \leq 54 mg/dL at \leq 0.5 hour, \leq 1 hour, \leq 2 hours, \leq 4 hours, >1 to \leq 2 hours, and >2 to \leq 4 hours following administration of MMTT containing 100 g of carbohydrates in patients with T1DM given either LYUMJEV or Humalog prior to the start of MMTT

(pre-meal) or 20 minutes after the start of MMTT (post-meal) are shown in Table 30 to Table 33. The median number of simulated BG \leq 70 mg/dL or BG \leq 54 mg/dL over the duration of the MMTT with 100 g of carbohydrate was predominantly higher compared to the number of events observed in patients with T1DM given LYUMJEV and Humalog prior to MMTT (premeal) and LYUMJEV after the start of MMTT (post meal) at Visit 18 in Trial ITRM. The relative risk of LYUMJEV to Humalog in the post-meal simulations was similar to or less than the relative ratio (RR) and relative difference (RD) values for the pre-meal simulations.

Table 30 Comparison of Observed and Model-Predicted Glucose \leq 70 mg/dL in Patients with T1DM Given LYUMJEV or Humalog Prior to the Start of MMTT (Pre-meal)

		Pre-meal Dose Administration					
		Number of glucose \leq 70 mg/dL					
		\leq 0.5 h	\leq 1 h	\leq 2 h	\leq 4 h	>1 to \leq 2 h	>2 to \leq 4 h
ITRM MMTT Visit 18	LY900014	31	50	62	108	12	46
	Humalog	15	19	22	56	3	34
	RR	2.07	2.63	2.82	1.93	4.00	1.35
	RD	16	31	40	52	9	12
Simulation 100 gm ^a	LY900014	69 (55 – 84)	78 (64 – 94)	101 (86 – 117)	113 (98 – 129)	23 (14 – 33)	12 (6 – 19)
	Humalog	59 (46 – 72)	63 (50 – 76)	78 (64 – 93)	99 (84 – 114)	15 (8 – 22)	21 (12 – 30)
	RR	1.17	1.24	1.29	1.14	1.53	0.57
	RD	10	15	23	14	8	-9

Abbreviations: gm = gram; h = hour; ITRM = Study ITRM; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T1DM = type 1 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles).

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.5.)

Table 31 Comparison of Observed and Model-Predicted Glucose ≤54 mg/dL in Patients with T1DM Given Either LYUMJEV or Humalog Prior to the Start of MMTT (Pre-meal)

		Pre-meal Dose Administration					
		Number of glucose ≤54 mg/dL					
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤4 h
ITRM MMTT Visit 18	LY900014	8	16	23	40	7	17
	Humalog	5	6	6	22	0	16
	RR	1.60	2.67	3.83	1.82	--	1.06
	RD	3	10	17	18	7	1
Simulation 100 gm ^a	LY900014	27 (18 - 37)	30 (21 - 41)	44 (32 - 56)	56 (42 - 69)	14 (7 - 21)	12 (6 - 19)
	Humalog	21 (13 - 29)	22 (14 - 30)	30 (21 - 41)	46 (35 - 58)	9 (4 - 14)	15 (8 - 24)
	RR	1.29	1.36	1.47	1.22	1.56	0.80
	RD	6	8	14	10	5	-3

Abbreviations: gm = gram; h = hour; ITRM = Study ITRM; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T1DM = type 1 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles).

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.6.)

Table 32 Comparison of Observed and Model-Predicted Glucose ≤70 mg/dL in Patients with T1DM Given Either LYUMJEV or Humalog 20 minutes after the Start of MMTT (Post-meal)

		Postmeal Dose Administration					
		Number of glucose ≤70 mg/dL					
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤4 h
ITRM MMTT Visit 18	LY900014	13	18	25	52	7	27
	LY900014	74 (59 - 88)	75 (59 - 89)	86 (72 - 101)	110 (94 - 126)	12 (6 - 19)	24 (15 - 34)
	Humalog	59 (46 - 73)	60 (46 - 73)	68 (54 - 82)	100 (83 - 116)	8 (4 - 15)	31 (22 - 42)
	RR	1.25	1.25	1.26	1.10	1.50	0.77
Simulation 100 gm ^a	RD	15	15	18	10	4	-7

Abbreviations: gm = gram; h = hour; ITRM = Study ITRM; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T1DM = type 1 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles).

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.7.)

Table 33 Comparison of Observed and Model-Predicted Glucose ≤54 mg/dL in Patients with T1DM Given Either LYUMJEV or Humalog 20 minutes after the Start of MMTT (Post-meal)

		Postmeal Dose Administration					
		Number of glucose ≤54 mg/dL					
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤4 h
ITRM MMTT Visit 18	LY900014	7	8	10	19	2	9
Simulation 100 gm^a	LY900014	30 (20 - 41)	31 (21 - 41)	38 (27 - 50)	58 (45 - 72)	7 (3 - 14)	20 (11 - 28)
	Humalog	17 (10 - 26)	17 (10 - 26)	21 (13 - 30)	47 (36 - 60)	4 (1 - 8)	26 (17 - 36)
	RR	1.76	1.82	1.81	1.23	1.75	0.77
	RD	13	14	17	11	3	-6

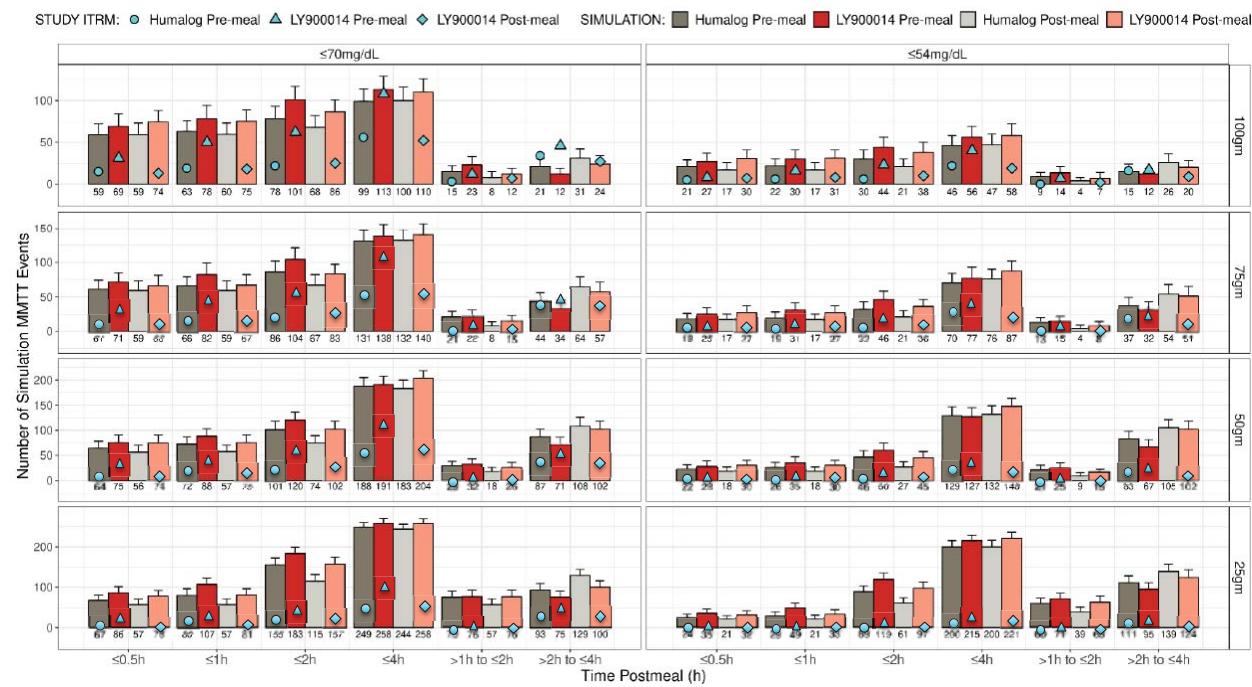
Abbreviations: gm = gram; h = hour; ITRM = Study ITRM; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T1DM = type 1 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles).

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.8.)

The sensitivity analysis (Figure 43) showed that simulated incidences of hypoglycemia were expectedly even higher when assuming 75 g, 50 g, and 25 g of carbohydrate amounts given with the insulin dose compared to a 100 g carbohydrate amounts.

Figure 43 Model-predicted Glucose ≤ 70 mg/dL (Left Column) or ≤ 54 mg/dL (Right Column) in Patients with T1DM following the MMTT Containing 100 gm (Top Row), 75 gm (Second Row), 50 gm (Third Row) or 25 gm (Bottom Row) of Carbohydrates and LYUMJEV or Humalog Given Immediately before the Meal (Pre-meal) or 20 Minutes after the Start of Meal (Post-meal). Study ITRM Observed Glucose Overlaid on Model-Predicted Glucose.



Abbreviations: gm = gram; MMTT = mixed meal tolerance test; T1DM = type 1 diabetes mellitus.

Note: The numbers below each bar along the x-axis are the median of the simulation and correspond to the height of each bar. The error bar is the 97.5th percentile of the 1000 replicates.

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Figure 4.4.)

Simulations in T2DM

Summaries of the number of simulated BG ≤ 70 mg/dL or BG ≤ 54 mg/dL at ≤ 0.5 hour, ≤ 1 hour, ≤ 2 hours, ≤ 4 hours, >1 to ≤ 2 hours, and >2 to ≤ 4 hours following administration of MMTT containing 100 g of carbohydrates in patients with T2DM given either LYUMJEV or Humalog prior to the start of MMTT (pre-meal) or 20 minutes after the start of MMTT (post-meal) are shown in Table 34 to Table 37. The median number of simulated BG ≤ 70 mg/dL or BG ≤ 54 mg/dL over the duration of the MMTT with 100 g of carbohydrate was predominantly higher compared to the number of events observed in patients with T2DM given LYUMJEV and Humalog prior to MMTT (pre-meal) at Visit 18 in Trial ITRN. The cumulative number of BG ≤ 70 mg/dL or BG ≤ 54 mg/dL during the ≤ 4 hours and the >1 -hour and ≤ 2 -hour time periods after the start of MMTT with 100 g of carbohydrates was slightly higher in those treated with LYUMJEV compared to those treated with Humalog. The relative risk of LYUMJEV to Humalog in the post-meal simulations was similar to or less than the RR and RD values for the pre-meal simulations.

Table 34 Comparison of Observed and Model-Predicted Glucose ≤70 mg/dL in Patients with T2DM Given Either LYUMJEV or Humalog Prior to the Start of MMTT (Pre-meal)

		Pre-meal Dose Administration					
		Number of glucose ≤70 mg/dL					
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤4 h
ITRN MMTT Visit 18	LY900014	8	12	14	28	2	14
	Humalog	5	7	8	15	1	7
	RR	1.60	1.71	1.75	1.87	2.00	2.00
	RD	3	5	6	13	1	7
Simulation 100 gm ^a	LY900014	8 (3 – 13)	8 (3 – 14)	13 (7 – 20)	24 (15 – 34)	5 (1 – 9)	10 (5 – 18)
	Humalog	7 (2 – 13)	7 (3 – 14)	9 (4 – 15)	19 (12 – 28)	1 (0 – 4)	10 (5 – 17)
	RR	1.14	1.14	1.44	1.26	5.00	1.00
	RD	1	1	4	5	4	0

Abbreviations: gm = gram; h = hour; ITRN = Study ITRN; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T2DM = type 2 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles).

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.1.)

Table 35 Comparison of Observed and Model-Predicted Glucose ≤54 mg/dL in Patients with T2DM Given Either LYUMJEV or Humalog Prior to the Start of MMTT (Pre-meal)

		Pre-meal Dose Administration					
		Number of glucose ≤54 mg/dL					
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤4 h
ITRN MMTT Visit 18	LY900014	1	3	5	9	2	4
	Humalog	1	2	2	3	0	1
	RR	1.00	1.50	2.50	3.00	--	4.00
	RD	0	1	3	6	2	3
Simulation 100 gm ^a	LY900014	1 (0 – 4)	1 (0 – 4)	3 (0 – 7)	7 (2 – 12)	2 (0 – 5)	3 (0 – 8)
	Humalog	1 (0 – 3)	1 (0 – 3)	2 (0 – 5)	5 (2 – 10)	1 (0 – 3)	4 (1 – 8)
	RR	1.00	1.00	1.50	1.40	2.00	0.75
	RD	0	0	1	2	1	-1

Abbreviations: gm = gram; h = hour; ITRN = Study ITRN; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T2DM = type 2 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles)

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.2.)

Table 36 Model-Predicted Glucose ≤70 mg/dL in Patients with T2DM Given Either LYUMJEV or Humalog 20 minutes after the Start of MMTT (Post-meal)

		Postmeal Dose Administration					
		Number of glucose ≤70 mg/dL					
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤4 h
Simulation 100 gm^a	LY900014	9 (4 – 16)	10 (4 – 16)	11 (5 – 18)	24 (15 – 34)	2 (0 – 5)	13 (6 – 20)
	Humalog	6 (2 – 11)	6 (2 – 11)	9 (4 – 14)	19 (12 – 28)	3 (0 – 6)	10 (5 – 17)
	RR	1.50	1.67	1.22	1.26	0.67	1.30
	RD	3	4	2	5	-1	3

Abbreviations: gm = gram; h = hour; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T2DM = type 2 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles).

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.3.)

Table 37 Model-Predicted Glucose ≤54 mg/dL in Patients with T2DM Given Either LYUMJEV or Humalog 20 minutes after the Start of MMTT (Post-meal)

		Postmeal Dose Administration					
		Number of glucose ≤54 mg/dL					
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤4 h
Simulation 100 gm^a	LY900014	2 (0 – 6)	2 (0 – 6)	3 (0 – 7)	6 (2 – 12)	1 (0 – 3)	3 (0 – 8)
	Humalog	0 (0 – 2)	0 (0 – 2)	2 (0 – 5)	6 (2 – 12)	1 (0 – 4)	4 (1 – 8)
	RR	--	--	1.50	1.00	1.00	0.75
	RD	2	2	1	0	0	-1

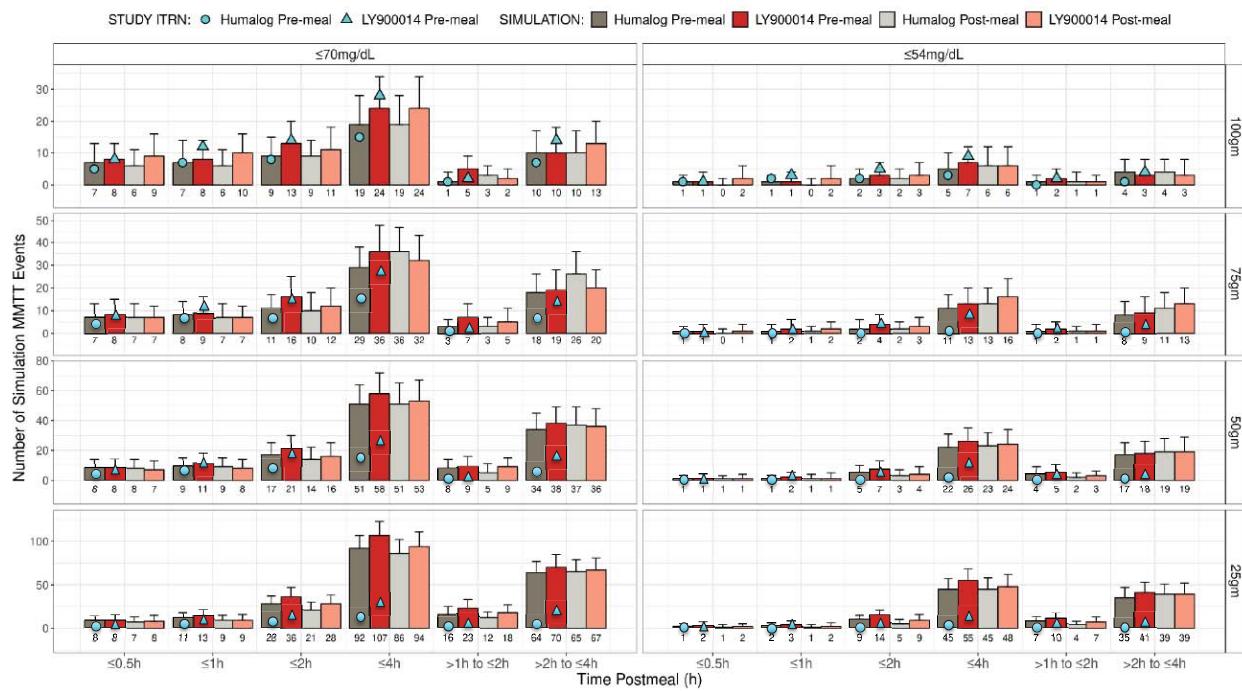
Abbreviations: gm = gram; h = hour; MMTT = mixed meal tolerance test; RD = relative difference calculated using Humalog median number of events subtracted from LY900014 median number of events; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T2DM = type 2 diabetes mellitus.

^a Median (2.5th to 97.5th percentiles).

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Table 4.4.)

The sensitivity analysis (Figure 44) showed that simulated incidences of hypoglycemia were expectedly higher when assuming 75 g, 50 g, and 25 g of carbohydrate amounts given with the insulin dose compared to a 100 g carbohydrate amounts.

Figure 44 Model-predicted Glucose ≤ 70 mg/dL (Left Column) or ≤ 54 mg/dL (Right Column) in Patients with T2DM following a MMTT Containing 100 gm (Top Row), 75 gm (Second Row), 50 gm (Third Row) or 25 gm (Bottom Row) of Carbohydrates and LYUMJEV or Humalog Given Immediately before the Meal (Pre-meal) or 20 Minutes after the Start of Meal (Post-meal). Study ITRN Observed Glucose Overlaid on Model-predicted Glucose.



Note: The numbers below each bar along the x-axis are the median of the simulation and correspond to the height of each bar. The error bar is the 97.5th percentile of the 1000 replicates.

Abbreviations: gm = gram; MMTT = mixed meal tolerance test; T2DM = type 2 diabetes mellitus.

(Source: Applicant's Response to the Agency's Information Request on 03/04/2020, Figure 4.2.)

Reviewer's Comments

With the assumption of 100 g carbohydrate intakes for all patients with T1DM in Phase 3 Trial ITRM, the modified IGI model predicted higher than the observed incidences of all documented hypoglycemia with BG ≤ 70 mg/dL or BG ≤ 54 mg/dL at ≤ 0.5 h, ≤ 1 h, ≤ 2 h and ≤ 4 h following the administration of LYUMJEV or Humalog immediately before the meal or LYUMJEV 20 minutes after the start of meal. In addition, the model predicted smaller difference in the incidence of all documented hypoglycemia than that observed in Trial ITRM between LYUMJEV and Humalog given immediately before the meal. This is probably due to the fact that the modified IGI model was developed solely based on Phase 1 MMTT Trial ITRV, where the treatment duration (single dose vs. 52-week multiple dose) and test meal (well controlled vs. uncontrolled) were different from the Phase 3 Trial ITRM. Moreover, individual carbohydrate consumption and insulin PK data was not collected in the Phase 3 trial ITRM. Although sensitivity analysis was conducted to evaluate the impact of different levels of carbohydrate intakes on the prediction of incidences of all documented hypoglycemia in patients with T1DM in Phase 3 Trial ITRM, such analysis is limited because the occurrence of hypoglycemia might also be affected by individual insulin PK level, glucose response, and carbohydrate consumption.

The Applicant's modified IGI model generally captured the incidences of all documented hypoglycemia with BG ≤ 70 mg/dL or BG ≤ 54 mg/dL at various time periods in patients with T2DM following

administration of either LYUMJEV or Humalog prior to the start of MTT containing 100 g of carbohydrates in Phase 3 Trial ITRN. The incidence of all documented hypoglycemia with BG ≤70 mg/dL or BG ≤54 mg/dL in patients with T2DM was generally low, despite the observation that the hypoglycemia incidence at ≤4 hours after meal tended higher for LYUMJEV compared to Humalog. The Applicant's simulation demonstrated low incidence of all documented hypoglycemia with BG ≤70 mg/dL or BG ≤54 mg/dL at various time periods for LYUMJEV post meal, which supports the proposed administration of LYUMJEV within 20 minutes after starting a meal in patients with T2DM from the safety perspective.

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/s/

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