Office of Clinical Pharmacology Review

BLA number	761109
Link to EDR	\\CDSESUB1\evsprod\BLA761109\0372
Receipt date	12/14/2021
Submission type	Efficacy supplement
Supplement number	4
Brand name	LYUMJEV™
Generic name	LY900014 (Insulin lispro-aabc)
Dosage form, route of administration and strength	Multiple dose injection and Continuous Subcutaneous Infusion (Insulin Pump) for LYUMJEV 100 units/mL (U-100)
Proposed indication	Indicated to improve glycemic control in adults and pediatric patients with diabetes mellitus.
Applicant	Eli Lilly and Company
OCP Review Team	Snehal Samant MS, PhD, Xiaolei Pan PhD, Justin Earp PhD, Jaya Vaidyanathan, PhD
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology

Table of Contents

1. EXECUTIVE SUMMARY

Lyumjev (LY900014, Insulin lispro-aabc) is a rapid-acting human insulin analog indicated for subcutaneous injection and intravenous infusion administration to improve glycemic control in adults with diabetes mellitus. Lyumjev is available in 2 dose strengths (100 and 200 units/mL) and approved for administration via subcutaneous injection, continuous subcutaneous insulin infusion (CSII), and intravenous (IV) infusion. The applicant (Eli Lilly and Company) has submitted an efficacy supplement to expand the indication to pediatric patients with diabetes mellitus.

The clinical development program for pediatrics includes one pharmacokinetic (PK)/ pharmacodynamic (PD) study (I8B-MC_ITSA) in children (≥ 6 years), adolescents and adults with Type 1 diabetes mellitus (T1DM) and one Phase 3 pivotal safety and efficacy trial (18B-MC-ITSB) in pediatric patients (≥ 6 to 18 years) with T1DM. The Sponsor has also submitted PK/PD modeling and simulation to support the use of Lyumjev in pediatric patients with type 2 diabetes mellitus (T2DM). The primary evidence of effectiveness of CSII for Lyumjev in pediatric patients with T1DM is provided by the Phase 3 trial which demonstrates non-inferiority of Lyumjev for the change in HbA1c from baseline to Week 26 compared to Humalog, which is a rapid acting insulin lispro approved as a CSII to improve glycemic control in diabetes mellitus. The PK/PD studies in patients with type 1 diabetes mellitus (T1DM) compare the PK of insulin lispro and post-prandial glucose excursion for Lyumjev compared to Humalog in children adolescent and adult patients with T1DM. Study ITSB was completed to fulfill PREA PMR 3874-1 for Lyumjev.

This review primarily focuses on the adequacy of the PK/PD studies and the modeling and simulation results as supportive evidence of effectiveness for Lyumjev in pediatric patients when administered via subcutaneous injection and CSII. In this document, the names LY900014 and Lyumjev are used interchangeably.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology (OCP/ DCEP) has reviewed the information contained in BLA 761109/ Supplement 4 and finds it acceptable to support approval of Lyumjev for use in pediatric patients (≥ 6 years to 18 years of age) with diabetes mellitus.

1.2 Post-Marketing Requirements and Commitments

None.

1.3 Summary of important clinical pharmacology findings

The following clinical pharmacology study was included in this submission to support the administration of Lyumjev by CSII:

- I8B-MC-ITRF [ITSA]: Study ITSA provides the PK and PD (post-prandial glucose excursion; PPG) of Lyumjev compared to Humalog given as a bolus either as a SC injection or via a CSII pump in children (≥ 6 years), adolescents and adults with T1DM.
- Two pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation reports:
    - Multiple daily injection (MDI) pediatric/adult population PK/PD report
    - CSII pediatric/adult PK/PD population report

All patients in ITSA received the same individualized bolus insulin dose for both Lyumjev and Humalog and, the content of their mixed meal tolerance test (MMTT) was kept the same throughout in crossover periods. The study and analyses are focused on the associated changes in PK and PD of Lyumjev as compared to Humalog. As Humalog is already approved in pediatric patients with T1DM and T2DM, this comparison provided supporting evidence for

Lyumjev as compared to Humalog and similarity in the safety profiles for the pediatric patient population.

Key clinical pharmacology findings:
For T1DM patients when insulin lispro were administered pre-meal:

- The median early 50% t_{max} of insulin lispro was reduced by approximately 30-51% with LY900014 compared to Humalog, which corresponds to a difference of 13 minutes in children, 7 minutes in adolescents, and 10 minutes in adults.
- Median time to reach peak maximal concentration (t_{max}) of serum insulin lispro was similar between children adolescents and adults between LY900014 and Humalog.
- The faster early insulin lispro absorption with LY900014 was associated with increase in early serum insulin lispro exposure, area under the concentration versus time curve from zero to 15 minutes post-dose ($AUC_{[0-15min]}$), by 6.5-fold in children, by 3.5-fold in adolescents, and by 5.1-fold in adults with LY900014 compared to Humalog.
- However, the overall mean serum insulin lispro systemic exposure (AUC[0-5h]), mean change from baseline [CFBL] AUC[0-5h] and mean time to maximal serum insulin lispro concentration were similar for Lyumjev compared to Humalog
- Consistent with the similarity in the PK profiles, the overall PPG excursions [0-5 h] after test meals were numerically higher(early) or comparable (overall) for Lyumjev compared to Humalog. No significant age group-by treatment interactions were identified.

For T1DM patients when insulin lispro were administered 20 minutes after the start of the meal:

- The model-predicted glucose profiles show a greater glucose-lowering effect with LY900014 than Humalog in children, adolescents, and adults with T2DM.

For T2DM patients via MDI:

- The model-predicted insulin lispro PK profiles in children and adolescents with T2DM showed an accelerated absorption and a reduction in the late insulin exposure with LY900014 compared to Humalog as observed in adults with T2DM.
- LY900014 and Humalog were predicted to have comparable hypoglycemia risks (≤ 70 mg/dL and ≤ 54 mg/dL) for all three age groups (children, adolescents, and adults) via either MDI therapy.

The results from study ITSA demonstrate that PK and PD (PPG) of insulin lispro was similar between Lyumjev and Humalog for patients with T1DM across the three age groups while still preserving the differences in the early (0-15 minutes) absorption when administered before meal. The similarity in PK and PD of Lyumjev and Humalog is consistent with the non-inferiority (non-inferiority margin of 0.4%) of Lyumjev (0.06%) compared to Humalog (0.09%) in the change from baseline to Week 26 in HbA1c as demonstrated the pivotal Phase 3 trial (18B-MC-ITSB). In addition, PopPK and PK/PD analyses confirmed that the differences in the time course of insulin lispro concentration for LY900014 and Humalog described the differences in the observed PPG response in pediatric patients with T1D on MDI and CSII therapy. The PK/PD model confirmed that the same PK/PD relationship remained, independent of adult or pediatric patients withT1DM, or whether LY900014 and Humalog was administered as MDI or CSII therapy. The PopPK and PK/PD analyses provided supporting evidence for extrapolation the indication from prior to the start of the meal to 20 minutes after the start of the meal, and from T1DM patients to T2DM patients in children, adolescents and adults.
Overall, the clinical pharmacology findings support the use of Lyumjev by CSII administration to improve glycemic control in pediatric patients (≥ 6 to 18 years) with diabetes mellitus.

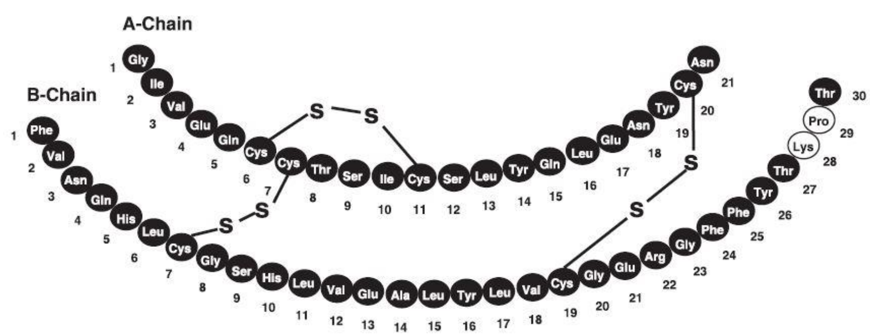
2. QUESTION BASED REVIEW

Eli Lilly and Company submitted a Biologics License Application (BLA) for Lyumjev 100 units/mL to the FDA seeking approval for subcutaneous administration via multiple daily injections (MDI) on August 15, 2019 (BLA 761109) and received FDA approval on June 15, 2020. Supplemental BLA for Lyumjev 100 units/mL in support of adding the continuous subcutaneous insulin infusion route of administration to the US prescribing information (USPI) was approved on August 13, 2021. This supplemental BLA provides the data supporting use of Lyumjev in pediatric patients with diabetes mellitus. This is an abridged version of the question-based review. For detailed review of Lyumjev, refer to the original BLA761109.

2.1 General attributes

2.1.1 What are the general attributes of Lyumjev and the drug product?

Lyumjev (insulin lispro-aabc injection) is a rapid-acting human insulin analog used to lower blood glucose. Insulin lispro is produced by recombinant DNA technology utilizing a nonpathogenic 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 $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808 Daltons, both identical to that of human insulin. Insulin lispro-aabc has the following primary structure:



LYUMJEV is a sterile, aqueous, clear, and colorless solution for subcutaneous or intravenous administration. Each mL of LYUMJEV U-100 contains 100 units of insulin lispro-aabc and the inactive ingredients: glycerol (12.1 mg), magnesium chloride hexahydrate (1.02 mg), metacresol (3.15 mg), sodium citrate dihydrate (4.41 mg), treprostinil sodium (1.06 mcg), zinc oxide (content adjusted to provide 39 mcg zinc ion), and Water for Injection, USP. The LY900014 drug product is supplied as a 100 unit/mL solution in (b) (4) glass 10 mL vial with an elastomeric stopper. For continuous subcutaneous insulin infusion (CSII), LY900014 drug product from the 10 mL vial is transferred to pump reservoir as per specific instructions from the CSII pump system manufacturer.

2.2 General Clinical Pharmacology/ Specific review questions

2.2.1 Does the clinical pharmacology data adequately support the administration of Lyumjev in pediatric patients and adolescents with Type 1 Diabetes Mellitus via subcutaneous injection and CSII?

Clinical pharmacology study, I8B-MC-ITSA (ITSA), provides supportive evidence in terms of the PK and PD profile of LY900014 when administered as a single subcutaneous (SC) bolus administered via injection and via continuous subcutaneous insulin infusion (CSII) in children (≥ 6 years) and adolescents with T1DM. The study specifically addresses whether the PK/PD profile of Lyumjev and the differences from Humalog observed with subcutaneous bolus via injection and CSII are consistent across children and adolescents compared to adults with T1DM and whether the data support the same time of administration and dose.

Study ITSA was a randomized, multi-center, patient- and investigator-blind, 2-part study, with each part containing a 2-period crossover assessment in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years) with T1DM to evaluate the insulin lispro PK and PD (post-prandial glucose excursion; PPG) characteristics of Lyumjev and Humalog given as a single dose bolus either as a SC injection or via a CSII pump. This study comprised 2 parts: Part A: Patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus injection; Part B: Patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus via CSII. Key inclusion criteria for this study were male or female subjects with a diagnosis of T1DM aged between ≥6 and <65 years, children and adolescents with a body mass index (BMI) within 3rd and 95th BMI percentiles with a minimum weight of 25 kg, adults with a BMI <28.0 kg/m2, and glycated hemoglobin ≤10% at screening.

The run-in period started with a variable intravenous (IV) infusion of glucose (5% dextrose solution) or regular human insulin to reach a target glucose level of 135±25 mg/dL (7.5±1.4 mmol/L). If this target glucose level was not attained before 11:00 AM on Day 1, MMTT was halted and performed on a separate visit (an MMTT can only be rescheduled (up to 7 days) once for each study period). The run-in period ends once the target blood glucose level was attained and remained stable without intervention for at least 20 minutes before the scheduled start time of MMTT on Day 1. A liquid MMTT was given to the children, adolescents, and adults for each period and completed within 15 minutes of starting the meal. Patients did not consume any further oral food until the completion of blood glucose collection (approximately 300 minutes). The MMTT was adjusted by the patient’s weight, unless they were greater than 55 kg and received a MMTT containing 100 g of carbohydrates. The MMTT was kept the same for both periods.

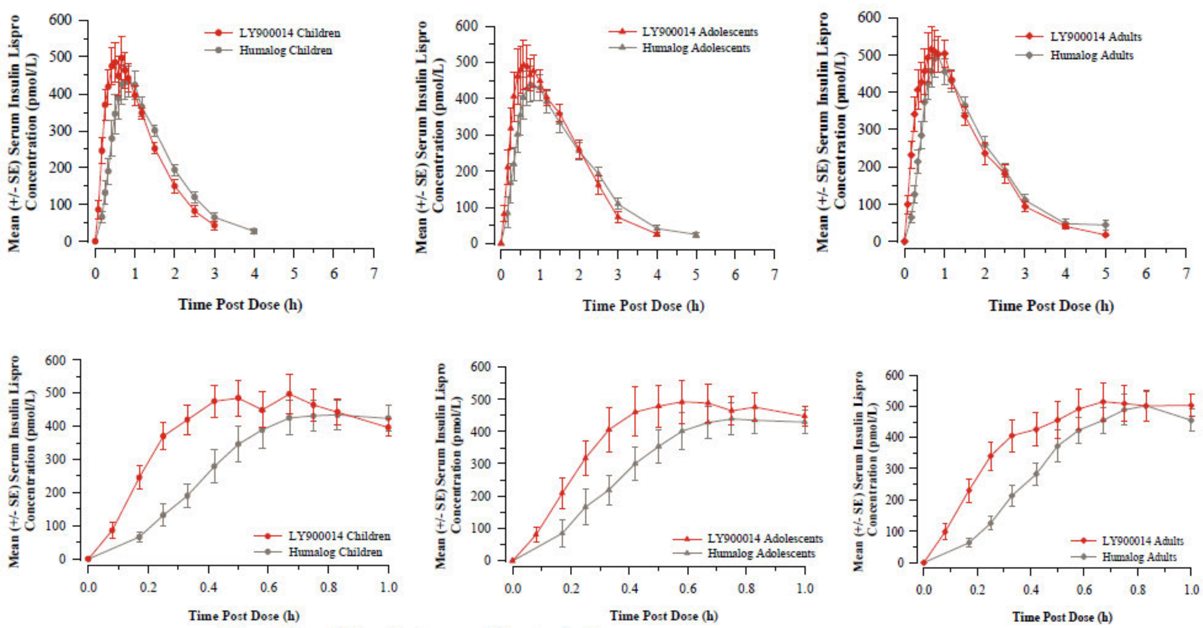
In part A, each patient received either LY900014 or Humalog with an insulin lispro dose level of 0.2 U/kg body weight, as a SC bolus injection per the assigned treatment sequence. The study drug was administered immediately before the start of a test meal per the assigned treatment sequence. This dose of insulin before the MMTTs for each patient was the same for each test meal throughout the crossover periods; this dose was maintained for the patient in Part B.

In Part B insulin U-100 was administered via Medtronic 640G or 630G CSII. The basal rate setting was standardized to 0.1 U/hour during the run-in period in Part B. Each patient received either LY900014 or Humalog with an insulin lispro dose level of 0.2 U/kg body weight, as a SC bolus dose delivered using the CSII pump per the assigned treatment sequence. The catheter was inserted the night before with low continuous delivery overnight. Patients received the assigned treatment immediately before each of the test meals. At the start of dosing period (Day 1), a standardized test meal was administered.

PK of insulin lispro following SC bolus injection administration

In Part A, the differences in insulin lispro PK profiles between LY900014 and Humalog following SC bolus injection were similar in children, adolescents, and adults. Median time to reach peak maximal concentration (t_{max}) of serum insulin lispro was similar between children (0.75 h), adolescents (0.79-0.83 h), and adults (0.83 h) between LY900014 and Humalog. (Appendix 4.2.2). The median early 50% t_{max} of insulin lispro was reduced by approximately 30-51% with LY900014 compared to Humalog, which corresponds to a difference of 13 minutes in children, 7 minutes in adolescents, and 10 minutes in adults. This slightly faster early insulin lispro absorption with LY900014 was associated with increase in early serum insulin lispro exposure, area under the concentration versus time curve from zero to 15 minutes post-dose ($AUC_{[0\text{-}15min]}$), by 6.5-fold in children, by 3.5-fold in adolescents, and by 5.1-fold in adults with LY900014 compared to Humalog. Similarly, the $AUC_{[0\text{-}30min]}$ was increased by 2.7-fold in children, by 1.9-fold in adolescents, and by 2.1-fold in adults with LY900014 compared to Humalog.

Although slightly faster early insulin absorption was observed for LY900014, the overall mean systemic exposures ($AUC_{[0\text{-}\infty]}$, $AUC_{[0\text{-}tlast]}$) of serum insulin lispro were not statistically significantly different for LY900014 compared to Humalog in all the age groups.

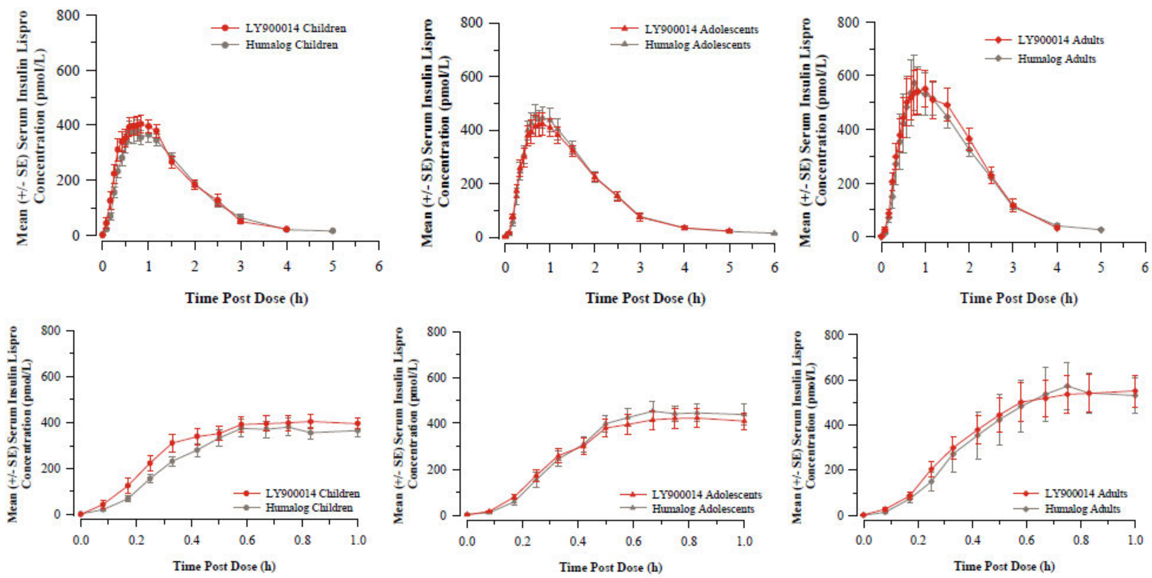


Abbreviations: SC = subcutaneous; SE = standard error.

Figure 1. Mean insulin lispro concentration (±SE) versus time (top) and for the first hour (bottom) following a 0.2-U/kg SC bolus injection of LY900014 or Humalog in children (left), adolescents (middle), and adults (right) with type 1 diabetes mellitus (Part A).
(Source: 18B-MC-ITSA CSR Figure ITSA 7.1, ITSA 7.2)

PK of insulin lispro following CSII administration

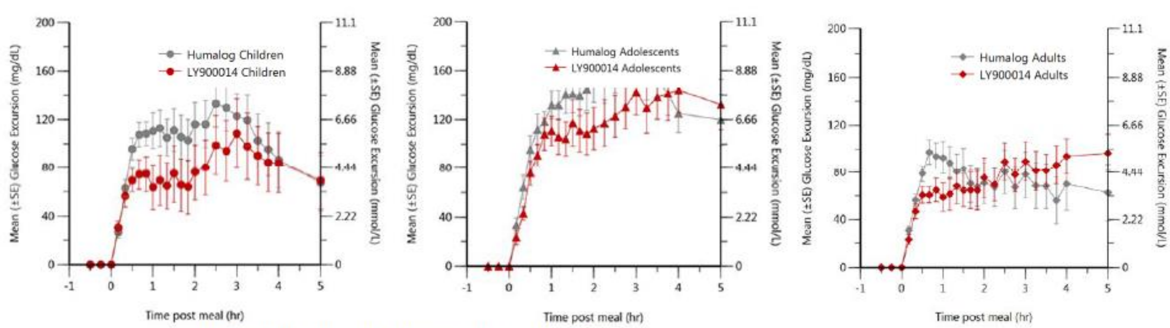
Median time to reach peak maximal concentration (t_{max}) of serum insulin lispro was similar between children (0.72-0.83 h), adolescents (0.67-0.83 h), and adults (0.88-0.92h) between LY900014 and Humalog. (Appendix 4.2.2). The timing of the early 50% tmax was reduced by 1 to 2 minutes and the onset of appearance was reduced by 0.5 to 1.52 minutes following LY900014 compared to Humalog in all age groups. The insulin lispro exposure within the first 15 minutes, AUC(0-15min) was increased by 1.61-fold in children ($p=0.0397$), by 1.38-fold in adolescents (p=0.1266), and 1.66-fold in adults (p=0.0229) after LY900014 administration compared to Humalog. The overall insulin exposure ($AUC_{[0-\infty]}$, $AUC_{[0-tlast]}$, or $AUC_{[0-7h]}$) and t_{max} were similar between LY900014 and Humalog in all the age groups.



Abbreviations: SC = subcutaneous; SE = standard error.

Figure 2. Mean insulin lispro concentration (±SE) versus time (top) and for the first hour (bottom) following a 0.2-U/kg SC bolus infusion of LY900014 or Humalog in children (left), adolescents (middle), and adults (right) with type 1 diabetes mellitus (Part B).
(Source: 18B-MC-ITSA CSR Figure ITSA 7.3, ITSA 7.4)

PD of insulin lispro following SC bolus injection administration



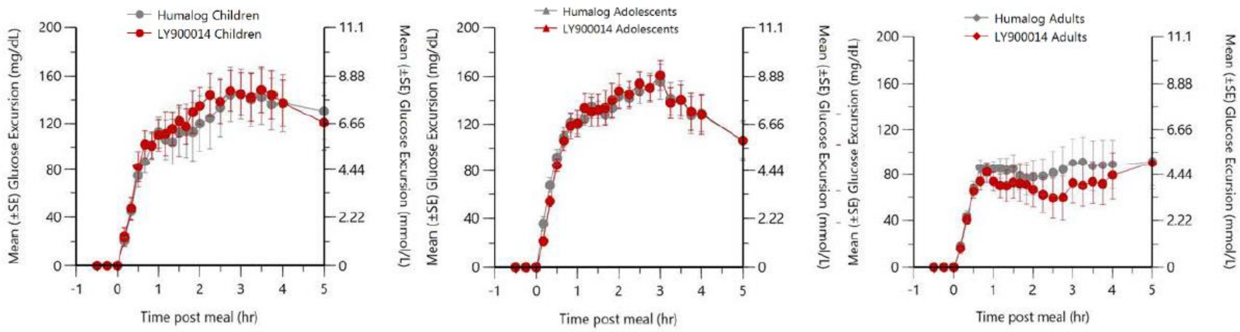
Abbreviations: SC = subcutaneous; SE = standard error.

Figure 3. Mean glucose excursions (±SE) versus time following a test meal with a 0.2-U/kg SC dose of LY900014 or Humalog in children (left), adolescents (middle), and adults (right) with type 1 diabetes mellitus (Part A). (Source: 18B-MC-ITSA CSR Figure ITSA 7.5)

LY900014 reduced the mean change from baseline postprandial glucose excursions up to 2 hours postmeal in both children and adolescent patients compared to Humalog. In adults, LY900014 reduced change from baseline postprandial glucose excursions up to 1-hour post-meal compared to Humalog.

LY900014 reduced the change from baseline blood glucose at 1 hour by 41.7 mg/dL in children, by 18.6 mg/dL in adolescents, and by 33.7 mg/dL in adults. Similarly, the change from baseline in blood glucose at 2 hour was reduced by 31.7 mg/dL in children and by 38.5 mg/dL in adolescents with LY900014 compared to Humalog.

PD of insulin lispro following CSII administration



Abbreviations: SC = subcutaneous; SE = standard error.

Figure 4. Mean glucose excursions (±SE) versus time following a test meal with a 0.2-U/kg SC dose of LY900014 or Humalog in children (left), adolescents (middle), and adults (right) with type 1 diabetes mellitus (Part B). (Source: 18B-MC-ITSA CSR Figure ITSA 7.6)

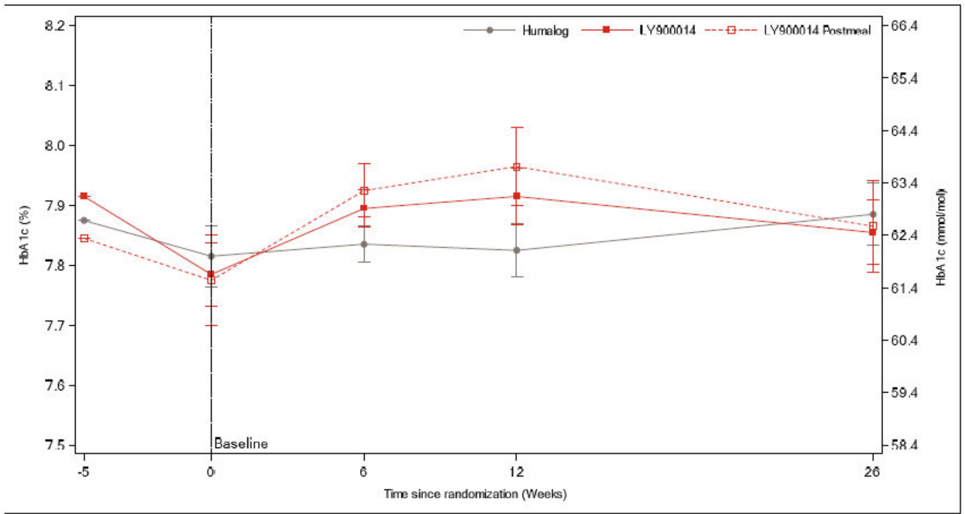
The postprandial glucose response between LY900014 and Humalog were similar in all age groups. No significant changes were identified between treatments.

Overall, the PD profiles were consistent with corresponding changes in PK for both, LY900014 and Humalog. Based on exploratory analysis of the interaction between age group and treatment effect, there were no significant age group-by treatment interactions. The PK/PD data from this study provide supportive evidence of adequacy of administration of Lyumjev in children (age 6 to <12 years), adolescents (age 12 to <18 years) by CSII and multiple dose injection.

2.2.2. What is the relevance of Lyumjev pharmacokinetic/pharmacodynamic data to the observations from the efficacy evaluation of Lyumjev in comparison to Humalog in the pivotal Phase 3 trial ITSB?

ITSB was a Phase 3, prospective, randomized, outpatient, multinational, multicenter, parallel, active-controlled study conducted in children and adolescent patients with type 1 diabetes currently using a multiple-daily-injection (MDI) regimen. The study included a 1-week screening with a 4-week lead-in period, followed by a 26-week treatment period and a 2-week safety follow-up period. daily injections. Both LY900014 and Humalog have the same insulin lispro concentration of 100 U/mL, and dosing is individualized for each patient. Patients in the LY900014 and Humalog treatment groups administered treatment 0 to 2 minutes before the start of a meal. Patients in the LY900014+20 treatment group administered treatment up to 20 minutes after the start of the meal. Primary objective was to test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (NIM = 0.4% for HbA1c) in patients 1 to <18 years of age with T1D when administered as prandial insulin (0 to 2 minutes prior to the meal) in combination with basal insulin as part of a multiple daily injection regimen for 26 weeks. While the acceptability of the efficacy/safety claims is deferred to Statistical/Clinical reviews, efficacy and PPG excursion results from the Phase 3 study ITSB are summarized here.

Figure 5 presents the actual LSM HbA1c by visit and at endpoint from all randomized patients from study entry to Week 26 for the efficacy estimand.



Abbreviations: LSMean = Least Square Mean; LY900014 Postmeal = LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal; SEM = Standard Error of Mean.

Note 1: The conversion between % and mmol/mol is 10.93*Hba1c(%) - 23.5
Note 2: Data are Mean at study entry and LSMean ± SEM at other visits.

Figure 5. HbA1c from screening to Week 26
(Source: 18B-MC-ITSB CSR Figure ITSB 5.1)

There were no significant differences in HbA1c between treatment groups at any visit.

At week 26, treatment with mealtime Lyumjev provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin (0.4%). Post-meal Lyumjev met the prespecified non-inferiority margin (0.4%) compared to mealtime Humalog. Insulin doses were similar in all treatment groups at baseline and at 26 weeks. LY900014 versus Humalog change from baseline in postprandial glucose excursion was statistically significantly lower for:

- morning premeal to 1-hour postmeal excursions (p=0.016): -14.5 [-0.8] versus -4.3 [-0.2].
- midday premeal to 1-hour postmeal excursions (p=0.004): -7.4 [-0.4] versus 5.4 [0.3].
- evening premeal to 1-hour postmeal excursions (p<0.001): -10.4 [-0.6] versus 5.7 [0.3].
- for premeal to 1-hour postmeal excursion daily mean (p<0.001): -11.3 [-0.6] versus 1.9 [0.1].

Source: 18B-MC-ITSB CSR

LY900014+20 versus LY900014 was statistically significantly higher for premeal to 1-hour post-meal excursion daily mean change from baseline (p=0.009): -2.5 [-0.1] versus -11.3 [-0.6]. There were no other significant differences between treatment groups for PPG at Week 26.

A statistically significant treatment difference for change from baseline in 1-hour and 2-hour PPG excursion after 26 weeks of treatment during a mixed meal tolerance test was observed in favor of Lyumjev when compared to Humalog. However, a similar reduction in HbA1c from baseline to Week 26 makes the difference in the extent of 1-hour and 2-hour PPG excursion not clinically meaningful. The non-inferiority reduction of HbA1C is ITSB is consistent with the comparable glycemic control observed between Lyumjev and Humalog in the PK/PD study ITSA.

2.2.3. Does the clinical pharmacology data adequately support the administration of Lyumjev 20 minutes after start of the meal in pediatric patients and adolescents with Type 1 Diabetes Mellitus via MDI or CSII therapies?

Population PK (PopPK) and PK/PD models were developed to characterize the observed serum insulin lispro and glucose dynamic following MDI or CSII therapies in T1DM patients with different age groups (children, adolescent and adults). These models were based on data from

ITSA Part A and Part B, in which Lyumjev and Humalog were administered before meal. In order to further assess the PK/PD profiles of insulin lispro in T1DM patients given 20 minutes after the start of the meal, which was not tested in the Study ITSA, simulations were performed using the final optimized pediatric/adult models to predict insulin lispro and glucose profiles when insulin lispro is administered 20 minutes after the start of the meal.

The results showed that, irrespective of relative time of insulin to start of the meal, the model predicted a greater glucose-lowering effect with LY900014 than Humalog in children, adolescents, and adults with T1DM (**Figure 6**).

Children	Adolescents	Adults

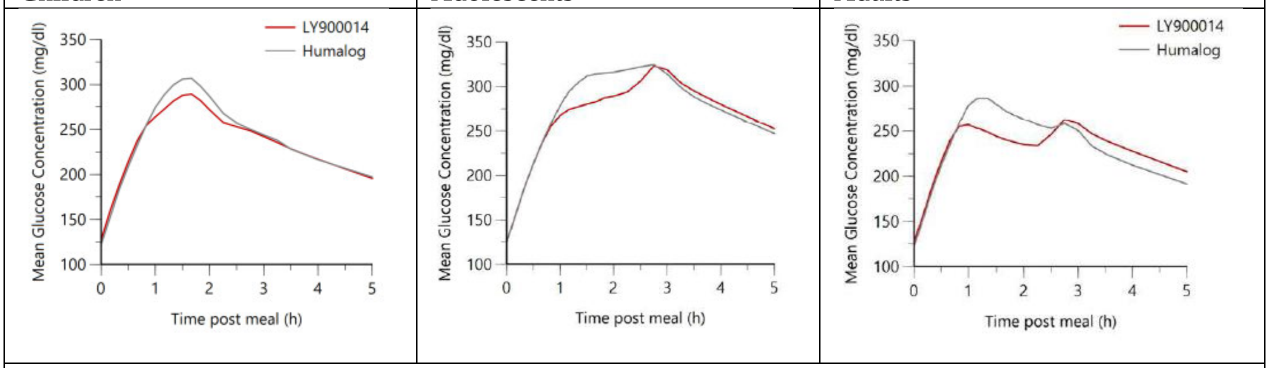


Figure 6. Model-predicted mean glucose concentration following SC injection of a 0.2 U/kg dose of either LY900014 or Humalog 20 minutes post the start of the meal in children (left), adolescents (middle), and adults (right) with T1DM.
Abbreviations: h = hour; MMTT = mixed meal tolerance test; SC = subcutaneous; T2D = type 2 diabetes mellitus.

Sources:
Applicant's MDI PopPK/PD report. Figure 10.1
Applicant's IR Response. Figure 9.1 (received on 3/28/2022).

2.2.4. Does the clinical pharmacology data adequately support the administration of Lyumjev in pediatric patients and adolescents with Type 2 Diabetes Mellitus via MDI or CSII therapies?

PopPK and PK/PD simulation were performed to characterize the serum insulin lispro profiles and plasma glucose profiles following MDI and CSII administration in T2DM patients.

PopPK simulations suggested that LY900014 has an accelerated insulin lispro absorption with a reduction in late insulin exposure compared to Humalog across all 3 age groups in T2DM patients (**Figure 7**). In addition, model-based PK/PD simulations showed that when both insulins (LY900014 and Humalog) were given prior to the start of meal or 20 minutes after the start of the meal, LY900014 had a greater glucose lowering effect than Humalog in children, adolescents and adults with T2DM (**Figure 8**). Moreover, the model predicted that the glucose excursion would be higher for both LY900014 and Humalog when given 20 minutes after the start of the meal compared to when LY900014 and Humalog are dosed immediately prior to the start of the meal (**Figure 8**). These observations align with the PPG response observed in clinical pharmacology studies conducted in adults with T2DM (Study -ITRW and Study I8B-FW-ITRH) where postmeal dosing was assessed for both LY900014 and Humalog and is reflective of the absorption of carbohydrates prior to the onset of insulin action. Finally, the hypoglycemia risks of LY900014 and Humalog were generally consistent across carbohydrate amounts. (**Figure 9**)

In general, the evidence from PK/PD modeling and simulations supported that LY900014 be used in pediatric patients with T2DM.

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Children	Adolescents	Adults

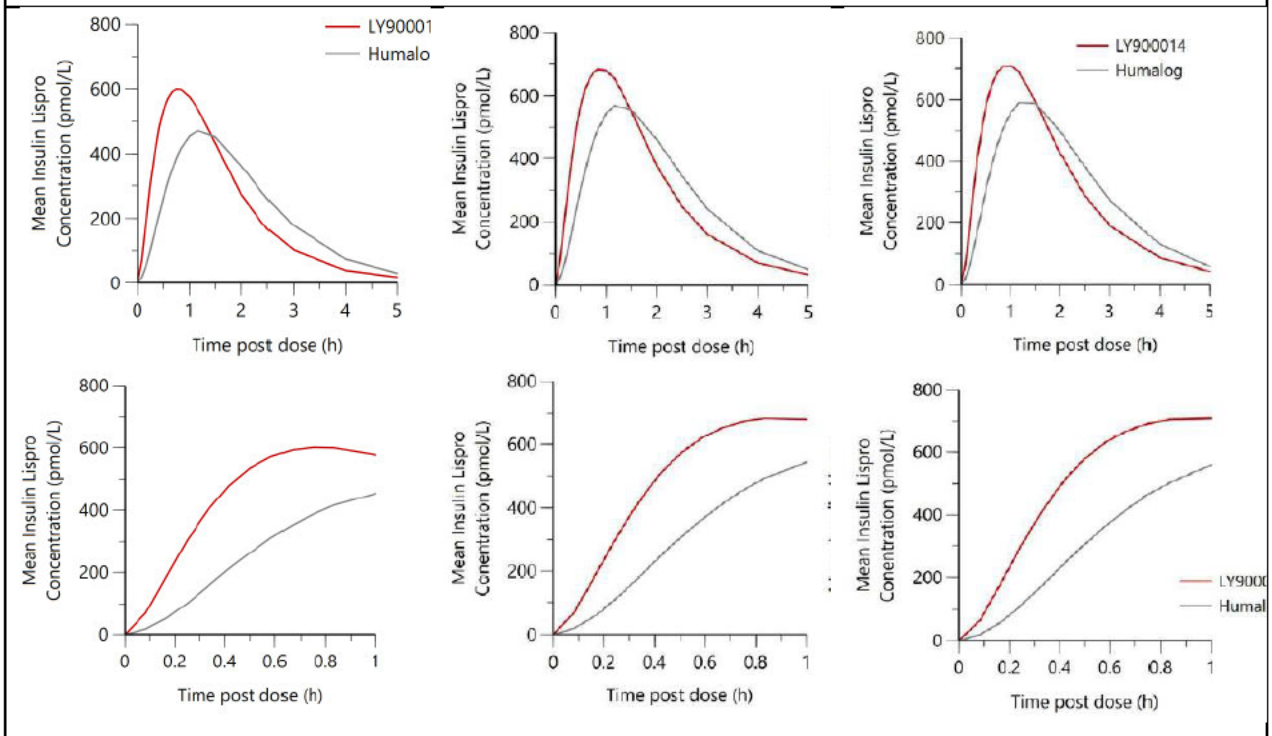


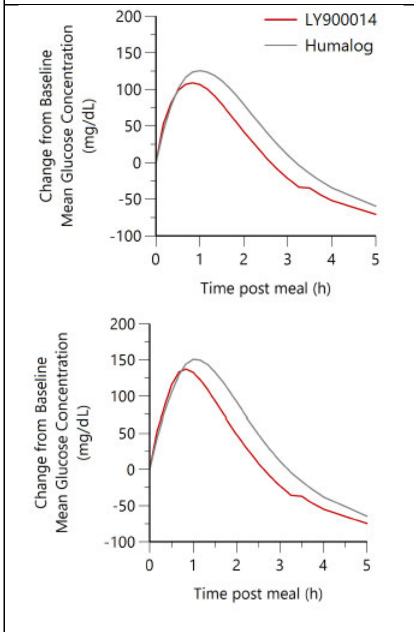
Figure 7. Model-predicted mean insulin lispro concentration versus time (top) and for the first hour post dose (bottom) following SC injection via MDI of a 0.2 U/kg dose of either LY900014 or Humalog in children (left), adolescents (middle), and adults (right) with T2DM.

Abbreviations: h = hour; SC = subcutaneous; T2D = type 2 diabetes mellitus.

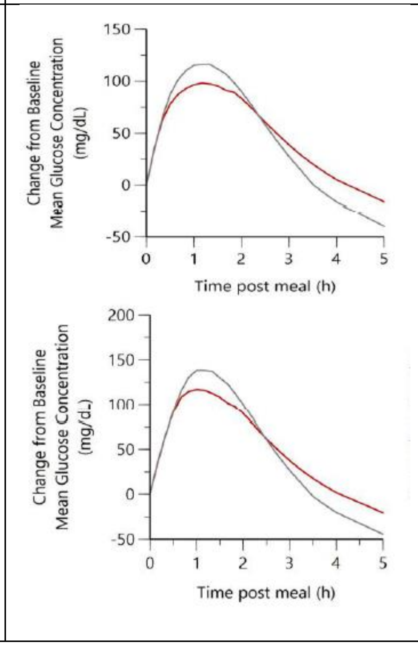
Source: Applicant's pediatric/adult MDI Population PK/PD reports. Figure 10.2.

Applicant's IR response on 03/28/2022. Figure 9.2

Children



Adolescents



Adults

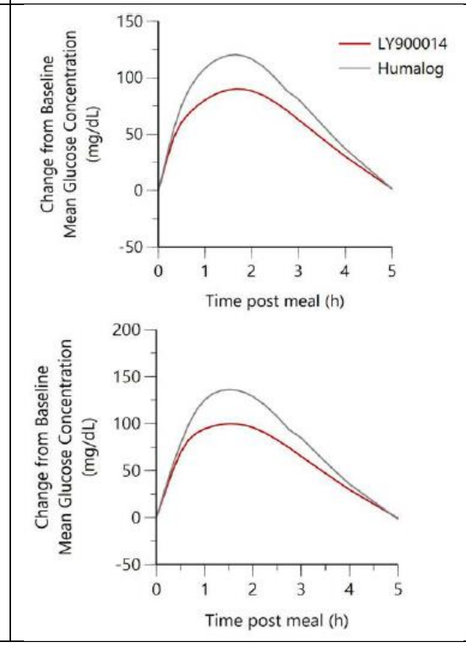


Figure 8. Model-simulated change from baseline glucose concentration versus time from breakfast MMTT following SC injection of a 0.2-U/kg dose of either LY900014 or Humalog when insulins are given immediately prior (top) and 20 minutes after (bottom) the start of the meal in children, adolescents, and adults with T2D.

Abbreviations: h = hour; SC = subcutaneous; T2D = type 2 diabetes mellitus.

Sources: Applicant's MDI PopPK/PD report. Figure 10.2
Applicant's IR Response. Figure 9.3 (received on 3/28/2022).

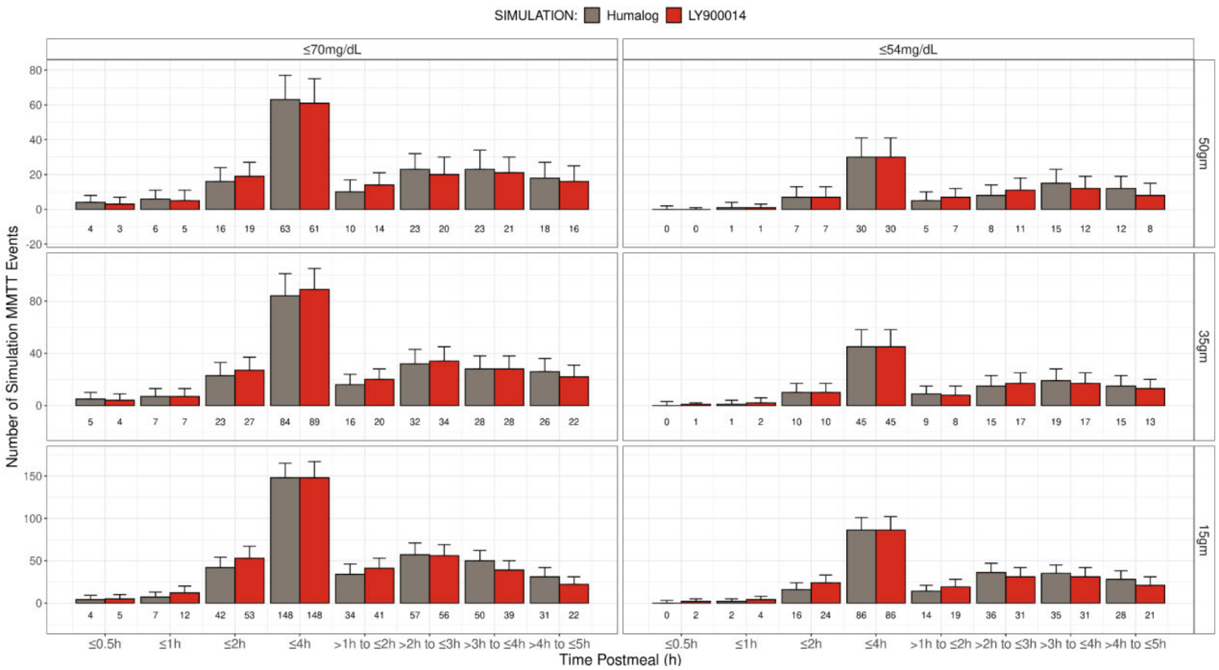


Figure 9. Model-predicted glucose ≤70 mg/dL (left column) or ≤54 mg/dL (right column) in children with T2DM following the MMTT containing 50 g (top row), 35 g (middle row), or 15 g (bottom row) of carbohydrates and LY900014 or Humalog given immediately before the meal at fixed dose of 10 U.
Abbreviations: MMTT = mixed meal tolerance test; T2DM = type 2 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 IR response on 7/15/2022. Table 5.4

3. LABELLING RECOMMENDATION

None

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Free insulin Lispro (LY275585) in human serum samples was analyzed using a validated enzyme-linked immunosorbent (ELISA) method at [redacted] (b) (4)

Table ITSA.5.3. Bioanalytical Method: Assay Parameters

Parameters	Insulin Lispro
LLOQ[a]	50 pg/mL (8.6 pM)
ULOQ[a]	2000.0 pg/mL (344.4 pM)
Inter-assay accuracy (% relative error)	-8.6 to – 0.7%
Inter-assay precision (% relative standard deviation)	6.2 to 11.2%
Stability	448 days at -20°C 365 days at -80°C

Abbreviations: LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.

[a] Samples above the limit of quantification were diluted to yield results within the calibrated range.

4.2 Clinical Study Report Synopsis: Study I8B-MC-ITSA

Title of Study: A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Compared to Humalog in Children, Adolescents, and Adults with Type 1 Diabetes Mellitus

Number of Investigators: This multi-centre study included 2 principal investigators.

Study Center(s): This study was conducted at 2 study centres in 2 countries.

Publication(s) Based on the Study: None at this time

Length of Study: Date of first patient entered: 27 March 2018 Date of last patient completed: 14 November 2019	**Phase of Development:** 1

Objectives:

Primary:

- Part A: To evaluate the pharmacokinetics (PK) of insulin lispro following a single subcutaneous (SC) bolus dose administered through injection of LY900014 compared to Humalog in children, adolescents, and adults with type 1 diabetes (T1DM).
- Part B: To evaluate the PK of insulin lispro following a single SC bolus dose administered through continuous subcutaneous insulin infusion (CSII) of LY900014 compared to Humalog in children, adolescents, and adults with T1DM.

Secondary:

- Parts A and B: To evaluate the difference in glucodynamic (GD) response to LY900014 and Humalog administered through SC bolus injection or CSII, as assessed using the liquid mixed meal tolerance test (MMTT) in children, adolescents, and adults with T1DM.
- Parts A and B: To evaluate the tolerability of LY900014 following SC injection or CSII in children, adolescents, and adults with T1DM.

Study Design: This was a multi-centre, Phase 1, randomised, 2-part, patient- and investigator-blind, 2-period crossover study in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years) with T1DM currently using a CSII pump or MDI regimen.

This study comprised 2 parts:

- Part A: Patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus injection.
- Part B: Patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus via CSII.

Number of Patients: Part A: Planned: 45 Randomized: 42 Treated (at least 1 dose): 42 Completed: 41	 Part B: Planned: 45 Randomized: 39 Treated (at least 1 dose): 37 Completed: 37

Diagnosis and Main Criteria for Inclusion: Key inclusion criteria for this study were male or female subjects with a diagnosis of T1DM aged between ≥6 and <65 years, children and adolescents with a body mass index (BMI) within 3rd and 95th BMI percentiles with a minimum weight of 25 kg, adults with a BMI <28.0 kg/m^2, and glycated hemoglobin ≤10% at screening.

Test Product, Dose, and Mode of Administration:

Part A: LY900014 was given as a single SC bolus injection; dose was prepared as 0.2 U/kg. The lot number was C746094D.

Part B: LY900014 was administered via Medtronic 640G or 630G CSII bolus; dose was prepared as 0.2 U/kg. The lot number was C746094D.

Comparator, Dose, and Mode of Administration:

Part A: Humalog was given as a single SC bolus injection; dose was prepared as 0.2 U/kg. The lot numbers were C558466A and C869764D.

Part B: Humalog was administered via Medtronic 640G or 630G CSII bolus; dose was prepared as 0.2 U/kg. The lot numbers were C558466A and C869764D.

Duration of Treatment:

Part A: The screening period was up to 28 days prior to dosing, the treatment period (2 periods) was 2 days as inpatient, and the follow-up period was 14 days after last dose. Total duration of each part was up to 68 days. Part B: The screening period was up to 28 days prior to dosing, the treatment period (2 periods) was 2 days as inpatient, and the follow-up period was 14 days after last dose. Total duration of each part was up to 68 days.

Variables:

Safety: Adverse events, injection/catheter insertion-site reactions, clinical laboratory parameters, vital signs, and hypoglycemic events.

Bioanalytical: Concentrations of insulin lispro were assayed using a validated enzyme-linked immunosorbent assay method specific for insulin lispro.

Pharmacokinetics: Serum insulin lispro concentrations were used to calculate several PK parameters including time to early half-maximal drug concentration (early 50% tmax), time to late half-maximal drug concentration (late 50% tmax), maximum observed drug concentration (Cmax), time of Cmax (tmax), area under the concentration versus time curve (AUC) from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-tlast]), AUC from time zero to 15 minutes (AUC[0-15min]), AUC from time zero to 30 minutes (AUC[0-30min]), AUC from time zero to 1 hour (AUC[0-1h]), AUC from time zero to 2 hours (AUC[0-2h]), AUC from time zero to 7 hours (AUC[0-7h]), AUC from time 2 to 7 hours (AUC[2-7h]), AUC from time 3 to 7 hours (AUC[3-7h]), AUC from time zero to infinity (AUC[0-∞]), onset of appearance (the time from study drug administration until the first time the serum insulin lispro concentrations reached the lower limit of quantification [LLOQ]) of insulin lispro in the serum, duration (the time from study drug administration until the serum insulin lispro concentrations reached the LLOQ in the terminal phase) of insulin lispro in the serum.

Glucodynamics: The incremental change from baseline glucose AUC values were calculated using the linear trapezoidal method (with negative areas included in the calculation of the trapezoidal areas). Several incremental change from baseline glucose AUCs were calculated: change from baseline glucose AUC from time 0 to 30 minutes postmeal (BGΔAUC[0-30min]), change from baseline glucose AUC from time 0 to 1 hour postmeal (BGΔAUC[0-1h]), change from baseline glucose AUC from time 0 to 2 hours postmeal (BGΔAUC[0-2h]), change from baseline glucose AUC from time 0 to 3 hours postmeal (BGΔAUC[0-3h]), change from baseline glucose AUC from time 0 to 4 hours postmeal (BGΔAUC[0-4h]), change from baseline glucose AUC from time 0 to 5 hours postmeal (BGΔAUC[0-5h])and change from baseline glucose AUC from time 2 to 5 hours postmeal (BGΔAUC[2-5h]). In addition, the change from baseline glucose at 1 hour (ΔBG1h), at 2 hours (ΔBG2h), and the maximum change from baseline glucose value (ΔBGmax) were also analyzed.

Statistical Evaluation Methods:

The analyses for Parts A and B were conducted separately using similar statistical methods. Primary statistical analyses were conducted on the set of patients who completed both treatment periods. Safety analyses were conducted for the set of patients receiving at least 1 dose of the study drug, whether or not they completed all protocol requirements.

Safety: All study drug- and protocol procedure-related adverse events were listed, and if the frequency of events allowed, safety data (including hypoglycaemic events) were summarised using descriptive methodology. Safety parameters were listed, and summarised using standard descriptive statistics.

Pharmacokinetics: Log-transformed PK parameters for insulin lispro were evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog, and their corresponding 95% confidence intervals (CIs) of the ratios using the mixed-effect model that included treatment, sequence, period, age group, and treatment by age group interaction as fixed effects and patient within sequence as a random effect. The same model without log transformation was used for the analysis of the PK time parameters (early 50% tmax, late 50% tmax, tmax). Least-squares means (LSmeans), treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences were estimated from the model. The treatment ratios and 95% CIs for the ratios using the Fieller's theorem are provided.

Glucodynamics:

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) were presented by treatment for each age group. The GD parameters on the original scale (not log transformed) were analysed using the same model used for PK parameters. Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences were estimated from the model. The treatment ratios and 95% CIs for the ratios were calculated using the Fieller's theorem.

Table ITSA.7.2. Statistical Analysis of the Pharmacokinetic Parameters Following SC Injection for Study I8B-MC-ITSA - Part A

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
Age group: Children						
Cmax (pmol/L)	Humalog	13	475			
	LY900014	13	520	1.09	(0.930, 1.29)	0.2704
AUC(0-∞) (pmol·h/L)	Humalog	13	759			
	LY900014	13	756	0.996	(0.916, 1.08)	0.9163
AUC(0-t_{last}) (pmol·h/L)	Humalog	13	744			
	LY900014	13	743	0.998	(0.916, 1.09)	0.9591
AUC(0-15min) (pmol·h/L)	Humalog	12	6.00			
	LY900014	13	39.1	6.52	(3.35, 12.7)	<.0001
AUC(0-30min) (pmol·h/L)	Humalog	13	52.9			
	LY900014	13	141	2.66	(1.90, 3.73)	<.0001
AUC(0-1h) (pmol·h/L)	Humalog	13	250			
	LY900014	13	354	1.42	(1.17, 1.72)	0.0009
AUC(0-2h) (pmol·h/L)	Humalog	13	556			
	LY900014	13	626	1.13	(0.992, 1.28)	0.0647
AUC(0-7h) (pmol·h/L)	Humalog	13	756			
	LY900014	13	755	0.999	(0.918, 1.09)	0.9813
AUC(2-7h) (pmol·h/L)	Humalog	13	169			
	LY900014	13	96.0	0.568	(0.438, 0.737)	<.0001
AUC(3-7h) (pmol·h/L)	Humalog	13	52.6			
	LY900014	13	21.9	0.416	(0.278, 0.624)	<.0001
Age group: Adolescents						
Cmax (pmol/L)	Humalog	14	485			
	LY900014	14	546	1.13	(0.963, 1.32)	0.1317
AUC(0-∞) (pmol·h/L)	Humalog	14	915			
	LY900014	14	961	1.05	(0.969, 1.14)	0.2228
AUC(0-t_{last}) (pmol·h/L)	Humalog	14	899			
	LY900014	14	950	1.06	(0.974, 1.15)	0.1788

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
AUC(0-15min) (pmol·h/L)	Humalog	13	7.49			
	LY900014	14	26.3	3.51	(1.85, 6.66)	0.0003
AUC(0-30min) (pmol·h/L)	Humalog	14	60.4			
	LY900014	14	118	1.95	(1.41, 2.71)	0.0002
AUC(0-1h) (pmol·h/L)	Humalog	14	264			
	LY900014	14	348	1.32	(1.09, 1.59)	0.0049
AUC(0-2h) (pmol·h/L)	Humalog	14	604			
	LY900014	14	714	1.18	(1.05, 1.33)	0.0084
AUC(0-7h) (pmol·h/L)	Humalog	14	908			
	LY900014	14	962	1.06	(0.976, 1.15)	0.1638
AUC(2-7h) (pmol·h/L)	Humalog	14	267			
	LY900014	14	199	0.746	(0.580, 0.958)	0.0230
AUC(3-7h) (pmol·h/L)	Humalog	14	92.2			
	LY900014	14	55.7	0.604	(0.409, 0.892)	0.0126
Age group: Adults						
Cmax (pmol/L)	Humalog	14	523			
	LY900014	14	561	1.07	(0.917, 1.25)	0.3688
AUC(0-∞) (pmol·h/L)	Humalog	14	987			
	LY900014	14	989	1.00	(0.924, 1.09)	0.9693
AUC(0-t_{last}) (pmol·h/L)	Humalog	14	965			
	LY900014	14	976	1.01	(0.931, 1.10)	0.7910
AUC(0-15min) (pmol·h/L)	Humalog	14	7.41			
	LY900014	14	37.8	5.11	(2.74, 9.54)	<.0001
AUC(0-30min) (pmol·h/L)	Humalog	14	62.9			
	LY900014	14	130	2.06	(1.49, 2.86)	<.0001
AUC(0-1h) (pmol·h/L)	Humalog	14	286			
	LY900014	14	362	1.27	(1.05, 1.53)	0.0148
AUC(0-2h) (pmol·h/L)	Humalog	14	648			
	LY900014	14	717	1.11	(0.980, 1.25)	0.0993
AUC(0-7h) (pmol·h/L)	Humalog	14	975			
	LY900014	14	987	1.01	(0.933, 1.10)	0.7623

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
AUC(2-7h) (pmol·h/L)	Humalog	14	290			
	LY900014	14	218	0.754	(0.587, 0.969)	0.0285
AUC(3-7h) (pmol·h/L)	Humalog	14	109			
	LY900014	14	68.4	0.629	(0.426, 0.928)	0.0208

Abbreviations: AUC = area under the concentration versus time curve; AUC(0-15min) = AUC 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) = AUC from time zero to 1 hour postdose; AUC(0-2h) = AUC from time zero to 2 hours postdose; AUC(0-7h) = AUC from time zero to 7 hours postdose; AUC(2-7h) = AUC from time 2 to 7 hours postdose; AUC(3-7h) = AUC from time 3 to 7 hours postdose; AUC(0-∞) = AUC from time zero to infinity; AUC(0-t_{last}) = AUC from time zero to time t, where t is the last time point with a measurable concentration; Cmax = Maximum observed drug concentration; CI = confidence interval; N = Number of patients; SC = subcutaneous.

Model: Log(PK) = Age Group + Period + Treatment + Sequence + Age Group*Treatment + Patient(Sequence) + Random Error where Patient(Sequence) is fitted as a random effect

Table ITSA.7.3. Statistical Analysis of the Pharmacokinetic Time Parameters Following SC Bolus Injection for Study I8B-MC-ITSA - Part A

Parameter	Treatment	N	LS mean	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)
Age group: Children								
tmax (h)	Humalog	13	0.843					
	LY900014	13	0.768	-0.0751	(-0.243, 0.092)	0.3697	0.911	(0.768, 1.09)
Early 50% tmax (min)	Humalog	13	25.4					
	LY900014	13	12.4	-13.0	(-17.8, -8.25)	<.0001	0.488	(0.359, 0.650)
Late 50% tmax (min)	Humalog	13	117					
	LY900014	13	99.5	-17.0	(-31.2, -2.87)	0.0198	0.854	(0.769, 0.934)
Duration (min)	Humalog	12	334					
	LY900014	13	278	-55.8	(-85.0, -26.5)	0.0006	0.833	(0.725, 0.948)
Onset of Appearance (min)	Humalog	13	6.45					
	LY900014	13	1.05	-5.40	(-8.06, -2.74)	0.0002	0.163	(0.061, 0.317)
Age group: Adolescents								
tmax (h)	Humalog	14	0.910					
	LY900014	14	0.891	-0.0186	(-0.180, 0.143)	0.8169	0.980	(0.789, 1.21)
Early 50% tmax (min)	Humalog	14	23.9					
	LY900014	14	16.6	-7.29	(-11.9, -2.72)	0.0026	0.695	(0.479, 0.914)
Late 50% tmax (min)	Humalog	14	131					
	LY900014	14	121	-10.2	(-23.8, 3.44)	0.1383	0.922	(0.805, 1.05)
Duration (min)	Humalog	11	349					
	LY900014	12	313	-36.1	(-66.7, -5.54)	0.0224	0.897	(0.795, 1.00)
Onset of Appearance (min)	Humalog	14	6.38					
	LY900014	14	1.91	-4.48	(-7.04, -1.91)	0.0011	0.299	(0.006, 0.633)
Age group: Adults								
tmax (h)	Humalog	14	0.904					
	LY900014	14	0.889	-0.0157	(-0.177, 0.146)	0.8447	0.983	(0.778, 1.23)
Early 50% tmax (min)	Humalog	14	24.5					
	LY900014	14	14.4	-10.1	(-14.6, -5.48)	<.0001	0.589	(0.421, 0.754)
Late 50% tmax (min)	Humalog	14	128					
	LY900014	14	117	-11.5	(-25.2, 2.13)	0.0956	0.910	(0.789, 1.04)
Duration (min)	Humalog	9	359					
	LY900014	13	343	-16.1	(-49.4, 17.1)	0.3281	0.955	(0.851, 1.06)
Onset of Appearance (min)	Humalog	14	4.84					
	LY900014	13	0.859	-3.98	(-6.60, -1.35)	0.0039	0.178	(0.055, 0.345)

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; SC = subcutaneous; tmax = time of maximum observed drug concentration.

Model: PK = Age Group + Period + Treatment + Sequence + Age Group*Treatment + 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.

Table ITSA.7.4. Summary of Key Pharmacokinetic Parameters (Geometric Mean [CV%]) of Insulin Lispro Following SC Bolus Infusion via Pump of LY900014 and Humalog in Children, Adolescents and Adults with Type 1 Diabetes Mellitus (Part B)

	Geometric Mean (CV% Geometric Mean)					
	Children		Adolescents		Adults	
PK Parameters	Humalog	LY900014	Humalog	LY900014	Humalog	LY900014
N	11	11	13	13	12	12
Mean Dose (U)	6.99	7.00	12.6	12.6	14.7	14.7
C_{max} (pmol/L)	400 (29)	450 (19)	478 (31)	433 (31)	548 (53)	563 (41)
t_{max}[a] (h)	0.73 (0.33 – 1.17)	0.83 (0.32 – 1.17)	0.67 (0.50 – 1.00)	0.83 (0.50 – 1.17)	0.92 (0.67 – 1.17)	0.88 (0.42 – 2.00)
Early 50% t_{max}[a] (min)	18.3 (9.05 – 24.7)	16.7 (7.36 – 30.5)	21.6[b] (11.5 – 27.6)	18.4 (12.8 – 30.2)	24.2 (12.9 – 37.3)	23.1 (14.6 – 28.2)
Late 50% t_{max}[a] (min)	115 (81.8 – 147)	117 (69.9 – 161)	128 (81.6 – 165)	124 (83.2 – 205)	141 (75.5 – 171)	136 (92.7 – 186)
AUC(0-15min) (pmol•h/L)	12.6 (58)	20.5 (68)	9.82 (77)	13.4 (59)	8.99 (95)	14.6 (79)
AUC(0-30min) (pmol•h/L)	74.0 (36)	95.6 (42)	75.8 (40)	76.6 (51)	68.4 (78)	89.5 (54)
AUC(0-1h) (pmol•h/L)	251 (29)	289 (30)	288 (31)	273 (38)	302 (56)	330 (46)
AUC(0-2h) (pmol•h/L)	530 (21)	570 (20)	611 (22)	590 (25)	722 (43)	775 (38)
AUC(0 -7h) (pmol•h/L)	714 (17)	743 (17)	866 (16)	842 (20)	1070 (35)	1100 (35)
AUC(2-7h) (pmol•h/L)	173 (36)	158 (44)	229 (56)	218 (59)	326 (30)	295 (52)
AUC(3-7h) (pmol•h/L)	58.9 (55)	50.2 (51)	86.1 (84)	75.2 (97)	115 (46)	83.8 (74)
AUC(0-t_{last}) (pmol•h/L)	706 (17)	730 (16)	858 (17)	833 (21)	1060 (35)	1090 (36)
AUC(0-∞) (pmol•h/L)	717 (17)	743 (17)	871 (16)	851 (21)	1070 (34)	1100 (35)
Onset of Appearance[a] (min)	2.08[c] (1.08 – 9.14)	1.33 (0.18 -5.96)	3.86[c] (1.64 – 7.98)	2.98[d] (0.957 – 6.23)	3.49 (1.14 – 10.0)	2.57[e] (0.472 – 10.7)
Duration[a] (min)	359[e] (298 – 420)	300 (240 – 420)	420[c] (240 – 420)	300[f] (240 – 360)	361[c] (360 – 420)	360[d] (300 – 420)

Abbreviations: AUC = area under the concentration versus time curve; AUC(0-15min) = AUC from time zero to 15 minutes; AUC(0-30min) = AUC from time zero to 30 minutes; AUC(0-1h) = AUC from time zero to 1 hour; AUC(0-2h) = AUC from time zero to 2 hour; AUC(0-7h) = AUC from time zero to 7 hour; AUC(2-7h) = AUC from time 2 hours to 7 hours; AUC(3-7h) = AUC from time 3 hours to 7 hours; AUC(0-t_{last}) = AUC from time zero to time t, where t is the last time point with a measurable concentration; AUC(0-∞) = AUC from time zero to infinity; C_{max} = maximum observed drug concentration; CV = coefficient of variation; 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; N = number of patient; Onset of Appearance = time from study drug administration until the first time serum insulin lispro concentrations reached the lower limit of quantification; PK= pharmacokinetics; SC = subcutaneous; t_{max} = time to maximum observed drug concentration.

a Median (minimum – maximum)

b N =12.

c N = 9.

d N = 11.

e N = 10.

f N = 7.

Table ITSA.7.5. Statistical Analysis of the Pharmacokinetic Parameters Following SC Bolus Infusion via Pump for Study I8B-MC-ITSA - Part B

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
Age group: Children						
Cmax (pmol/L)	Humalog	11	400			
	LY900014	11	448	1.12	(0.937, 1.34)	0.2035
AUC(0-∞) (pmol·h/L)	Humalog	11	717			
	LY900014	11	746	1.04	(0.959, 1.13)	0.3292
AUC(0-t_{last}) (pmol·h/L)	Humalog	11	706			
	LY900014	11	732	1.04	(0.955, 1.13)	0.3733
AUC(0-15min) (pmol·h/L)	Humalog	11	12.8			
	LY900014	11	20.5	1.61	(1.02, 2.53)	0.0397
AUC(0-30min) (pmol·h/L)	Humalog	11	74.7			
	LY900014	11	95.2	1.28	(0.899, 1.81)	0.1669
AUC(0-1h) (pmol·h/L)	Humalog	11	252			
	LY900014	11	288	1.14	(0.910, 1.44)	0.2407
AUC(0-2h) (pmol·h/L)	Humalog	11	530			
	LY900014	11	570	1.08	(0.941, 1.23)	0.2730
AUC(0-7h) (pmol·h/L)	Humalog	11	714			
	LY900014	11	745	1.04	(0.962, 1.13)	0.2952
AUC(2-7h) (pmol·h/L)	Humalog	11	173			
	LY900014	11	160	0.926	(0.759, 1.13)	0.4380
AUC(3-7h) (pmol·h/L)	Humalog	11	58.9			
	LY900014	11	51.2	0.869	(0.628, 1.20)	0.3873
Age group: Adolescents						
Cmax (pmol/L)	Humalog	13	478			
	LY900014	13	435	0.909	(0.771, 1.07)	0.2467
AUC(0-∞) (pmol·h/L)	Humalog	13	871			
	LY900014	13	848	0.974	(0.904, 1.05)	0.4784
AUC(0-t_{last}) (pmol·h/L)	Humalog	13	859			
	LY900014	13	831	0.968	(0.898, 1.04)	0.3963
AUC(0-15min) (pmol·h/L)	Humalog	13	9.71			
	LY900014	13	13.4	1.38	(0.909, 2.09)	0.1266

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
AUC(0-30min) (pmol·h/L)	Humalog	13	75.2			
	LY900014	13	76.9	1.02	(0.741, 1.41)	0.8871
AUC(0-1h) (pmol·h/L)	Humalog	13	288			
	LY900014	13	273	0.950	(0.770, 1.17)	0.6238
AUC(0-2h) (pmol·h/L)	Humalog	13	611			
	LY900014	13	591	0.967	(0.854, 1.09)	0.5808
AUC(0-7h) (pmol·h/L)	Humalog	13	866			
	LY900014	13	840	0.970	(0.901, 1.04)	0.4052
AUC(2-7h) (pmol·h/L)	Humalog	13	229			
	LY900014	13	216	0.940	(0.783, 1.13)	0.4970
AUC(3-7h) (pmol·h/L)	Humalog	13	86.2			
	LY900014	13	74.1	0.860	(0.637, 1.16)	0.3104
Age group: Adults						
Cmax (pmol/L)	Humalog	12	548			
	LY900014	12	567	1.03	(0.871, 1.23)	0.6957
AUC(0-∞) (pmol·h/L)	Humalog	12	1072			
	LY900014	12	1092	1.02	(0.943, 1.10)	0.6193
AUC(0-t_{last}) (pmol·h/L)	Humalog	12	1057			
	LY900014	12	1083	1.02	(0.946, 1.11)	0.5442
AUC(0-15min) (pmol·h/L)	Humalog	12	8.77			
	LY900014	12	14.6	1.66	(1.08, 2.57)	0.0229
AUC(0-30min) (pmol·h/L)	Humalog	12	67.3			
	LY900014	12	90.2	1.34	(0.958, 1.88)	0.0849
AUC(0-1h) (pmol·h/L)	Humalog	12	300			
	LY900014	12	332	1.11	(0.888, 1.38)	0.3561
AUC(0-2h) (pmol·h/L)	Humalog	12	723			
	LY900014	12	775	1.07	(0.942, 1.22)	0.2811
AUC(0-7h) (pmol·h/L)	Humalog	12	1066			
	LY900014	12	1092	1.02	(0.948, 1.11)	0.5314
AUC(2-7h) (pmol·h/L)	Humalog	12	327			
	LY900014	12	288	0.881	(0.728, 1.07)	0.1850
AUC(3-7h) (pmol·h/L)	Humalog	12	115			
	LY900014	12	81.0	0.703	(0.515, 0.961)	0.0283

Abbreviations: AUC = area under the concentration versus time curve; AUC(0-1h) = AUC from time zero to 1 hour postdose; AUC(0-2h) = AUC from time zero to 2 hours postdose; AUC(0-7h) = AUC from time zero to 7 hours postdose; AUC(2-7h) = AUC from time 2 to 7 hours postdose; AUC(3-7h) = AUC from time 3 to 7 hours postdose; AUC(0-15min) = AUC from time zero to 15 minutes postdose; AUC(0-30min) = AUC from time zero to 30 minutes postdose; AUC(0-∞) = AUC from time zero to infinity; AUC(0-t_{last}) = AUC from time zero to time t, where t is the last time point with a measurable concentration; Cmax = Maximum observed drug concentration; CI = Confidence interval; N = Number of patients; SC = subcutaneous.

Model: Log(PK) = Age Group + Period + Treatment + Sequence + Age Group*Treatment + Patient(Sequence) + Random Error where Patient(Sequence) is fitted as a random effect

Table ITSA.7.6. Statistical Analysis of the Pharmacokinetic Time Parameters for Study I8B-MC-ITSA - Part B

Parameter	Treatment	N	LS mean	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)
Age group: Children								
tmax (h)	Humalog	11	0.743					
	LY900014	11	0.806	0.0625	(-0.139, 0.264)	0.5325	1.08	(0.839, 1.40)
Early 50% tmax (min)	Humalog	11	18.3					
	LY900014	11	16.6	-1.65	(-6.46, 3.15)	0.4879	0.909	(0.686, 1.17)
Late 50% tmax (min)	Humalog	11	120					
	LY900014	11	112	-7.09	(-29.2, 15.1)	0.5188	0.941	(0.800, 1.09)
Duration (min)	Humalog	10	347					
	LY900014	11	317	-30.0	(-58.7, -1.36)	0.0408	0.914	(0.821, 1.01)
Onset of Appearance (min)	Humalog	9	2.95					
	LY900014	11	2.14	-0.812	(-2.45, 0.831)	0.3182	0.725	(0.367, 1.46)
Age group: Adolescents								
tmax (h)	Humalog	13	0.734					
	LY900014	13	0.858	0.124	(-0.061, 0.310)	0.1828	1.17	(0.877, 1.56)
Early 50% tmax (min)	Humalog	12	20.8					
	LY900014	13	19.8	-1.01	(-5.52, 3.50)	0.6504	0.951	(0.714, 1.24)
Late 50% tmax (min)	Humalog	13	122					
	LY900014	13	130	8.28	(-12.1, 28.7)	0.4138	1.07	(0.845, 1.34)
Duration (min)	Humalog	9	382					
	LY900014	7	315	-66.9	(-103, -30.5)	0.0008	0.825	(0.723, 0.947)
Onset of Appearance (min)	Humalog	9	4.58					
	LY900014	11	3.07	-1.52	(-3.27, 0.233)	0.0869	0.669	(0.421, 0.977)
Age group: Adults								
tmax (h)	Humalog	12	0.926					
	LY900014	12	0.955	0.0296	(-0.164, 0.223)	0.7578	1.03	(0.838, 1.21)
Early 50% tmax (min)	Humalog	12	24.5					
	LY900014	12	21.8	-2.75	(-7.37, 1.87)	0.2333	0.888	(0.768, 1.02)
Late 50% tmax (min)	Humalog	12	136					
	LY900014	12	137	1.66	(-19.6, 22.9)	0.8747	1.01	(0.867, 1.18)

Parameter	Treatment	N	LS mean	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)
Duration (min)	Humalog	9	391					
	LY900014	11	346	-45.3	(-75.4, -15.3)	0.0048	0.884	(0.807, 0.962)
Onset of Appearance (min)	Humalog	12	4.25					
	LY900014	10	3.72	-0.530	(-2.12, 1.06)	0.5000	0.875	(0.482, 1.44)

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 = Age Group + Period + Treatment + Sequence + Age Group*Treatment + 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

Table ITSA.7.7. **Summary of Key Change from Baseline in Glucodynamic Parameters (Arithmetic Mean [Standard Deviation]) Following Administration of Humalog and LY900014 in Children, Adolescents, and Adults with Type 1 Diabetes (Excluding Data after Any Treatment Intervention) in Part A**

	Arithmetic Mean (Standard Deviation)					
	Children		Adolescents		Adults	
PK Parameters	**Humalog**	**LY900014**	**Humalog**	**LY900014**	**Humalog**	**LY900014**
N	12	12	13	13	14	14
Mean Dose (U)	7.08	7.08	12.5	12.5	15.4	15.4
ΔBG_{max}	162	146	195	183	146	143
(mg/dL)	(51.5)	(66.3)	(66.8)	(61.4)	(51.5)	(39.3)
ΔBG_{1h}	111	63.7	132	111	92.4	58.7
(mg/dL)	(51.9)	(64.0)	(41.1)	(42.7)	(51.3)	(45.1)
ΔBG_{2h}	116	76.1	150	103[a]	70.8	75.3
(mg/dL)	(62.6)	(79.0)	(59.2)	(53.0)	(64.9)	(63.8)
BGΔAUC(0-30min)	22.9	20.5	24.2	17.4	21.1	16.7
(mg•h/dL)	(8.37)	(9.41)	(11.8)	(8.46)	(5.53)	(7.27)
BGΔAUC(0-1h)	76.1	56.4	81.5	66.1	67.1	47.5
(mg•h/dL)	(21.3)	(29.9)	(28.9)	(26.0)	(22.7)	(18.5)
BGΔAUC(0-2h)	185	125	222	162[a]	146	113
(mg•h/dL)	(71.1)	(99.5)	(76.5)	(64.6)	(76.1)	(68.3)
BGΔAUC(0-3h)	309	249[b]	381	277[a]	235[c]	192
(mg•h/dL)	(131)	(141)	(134)	(116)	(121)	(109)
BGΔAUC(0-4h)	390[b]	390[d]	529	407[a]	313[c]	277
(mg•h/dL)	(190)	(180)	(188)	(165)	(157)	(149)
BGΔAUC(0-5h)	420[d]	493[d]	651	537[a]	391[c]	372
(mg•h/dL)	(233)	(228)	(238)	(212)	(196)	(179)
BGΔAUC(2-5h)	252[d]	344[d]	430	376[a]	238[c]	260
(mg•h/dL)	(177)	(158)	(180)	(170)	(166)	(149)

Abbreviations: BGΔAUC(0-30min) = change from baseline glucose area under the concentration versus time curve from time zero to 30 minutes postmeal; BGΔAUC(0-1h) = change from baseline glucose area under the concentration versus time curve from time zero to 1 hour postmeal; BGΔAUC(0-2h) = change from baseline glucose area under the concentration versus time curve from time zero to 2 hours postmeal; BGΔAUC(0-3h) = change from baseline glucose area under the concentration versus time curve from time zero to 3 hours postmeal; BGΔAUC(0-4h) = change from baseline glucose area under the concentration versus time curve from time zero to 4 hours postmeal; BGΔAUC(0-5h) = change from baseline glucose area under the concentration versus time curve from time zero to 5 hours postmeal; BGΔAUC(2-5h) = change from baseline glucose area under the concentration versus time curve from time 2 to 5 hours postmeal; ΔBG_{1h} = change from baseline glucose at 1 hour; ΔBG_{2h} = change from baseline glucose at 2 hours; ΔBG_{max} = maximum change from baseline glucose value; N = number of patients; SD = standard deviation.

a N = 12.

b N = 11.

c N = 13.

d N = 10.

Table ITSA.7.8. Summary of Key Change from Baseline in Glucodynamic Parameters (Arithmetic Mean [Standard Deviation]) Following Administration of Humalog and LY900014 in Children, Adolescents, and Adults with Type 1 Diabetes (LOCF) - Part A

	Arithmetic Mean (Standard Deviation)					
	Children		Adolescents		Adults	
PK Parameters	Humalog	LY900014	Humalog	LY900014	Humalog	LY900014
N	12	12	13	13	14	14
Mean Dose (U)	7.08	7.08	12.5	12.5	15.4	15.4
BGΔAUC(0-30min)	22.9	20.5	24.2	17.4	21.1	16.7
(mg•h/dL)	(8.37)	(9.41)	(11.8)	(8.46)	(5.53)	(7.27)
BGΔAUC(0-1h)	76.1	56.4	81.5	66.1	67.1	47.5
(mg•h/dL)	(21.3)	(29.9)	(28.9)	(26.0)	(22.7)	(18.5)
BGΔAUC(0-2h)	185	125	222	176	146	113
(mg•h/dL)	(71.1)	(99.5)	(76.5)	(79.8)	(76.1)	(68.3)
BGΔAUC(0-3h)	309	216	381	300	218	192
(mg•h/dL)	(131)	(178)	(134)	(139)	(133)	(109)
BGΔAUC(0-4h)	415	308	529	438	285	277
(mg•h/dL)	(200)	(258)	(188)	(194)	(186)	(149)
BGΔAUC(0-5h)	492	384	651	577	351	372
(mg•h/dL)	(270)	(335)	(238)	(247)	(240)	(179)
BGΔAUC(2-5h)	307	260	430	401	205	260
(mg•h/dL)	(207)	(247)	(180)	(187)	(201)	(149)

Abbreviations: BGΔAUC(0-30min) = change from baseline glucose area under the concentration versus time curve from time zero to 30 minutes postmeal; BGΔAUC(0-1h) = change from baseline glucose area under the concentration versus time curve from time zero to 1 hour postmeal; BGΔAUC(0-2h) = change from baseline glucose area under the concentration versus time curve from time zero to 2 hours postmeal; BGΔAUC(0-3h) = change from baseline glucose area under the concentration versus time curve from time zero to 3 hours postmeal; BGΔAUC(0-4h) = change from baseline glucose area under the concentration versus time curve from time zero to 4 hours postmeal; BGΔAUC(0-5h) = change from baseline glucose area under the concentration versus time curve from time zero to 5 hours postmeal; BGΔAUC(2-5h) = change from baseline glucose area under the concentration versus time curve from time 2 to 5 hours postmeal; ΔBG_{1h} = change from baseline glucose at 1 hour; ΔBG_{2h} = change from baseline glucose at 2 hours; ΔBG_{max} = maximum change from baseline glucose value; LOCF = last observation carried forward; N = number of patients; SD = standard deviation.

a N = 12.

Table ITSA.7.10. Statistical Analysis of the Glucodynamic Parameters for Study I8B-MC-ITSA - Part A (Last Observation Carried Forward)

Parameter	Treatment		N	LS mean	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)
Age group: Children									
Glucose ΔAUC(0-30min)	Humalog		12	22.77					
(mg·h/dL)	LY900014		12	20.68	-2.09	(-7.28, 3.10)	0.4196	0.91	(0.69, 1.16)
Glucose ΔAUC(0-1h)	Humalog		12	75.17					
(mg·h/dL)	LY900014		12	57.64	-17.52	(-32.83, -2.21)	0.0261	0.77	(0.55, 1.02)
Glucose ΔAUC(0-2h)	Humalog		12	180.69					
(mg·h/dL)	LY900014		12	130.67	-50.02	(-95.24, -4.80)	0.0311	0.72	(0.46, 1.00)
Glucose ΔAUC(0-3h)	Humalog		12	302.61					
(mg·h/dL)	LY900014		12	226.61	-75.99	(-154.17, 2.19)	0.0564	0.75	(0.46, 1.03)
Glucose ΔAUC(0-4h)	Humalog		12	405.90					
(mg·h/dL)	LY900014		12	322.81	-83.09	(-193.27, 27.09)	0.1348	0.80	(0.49, 1.10)
Glucose ΔAUC(0-5h)	Humalog		12	481.38					
(mg·h/dL)	LY900014		12	403.04	-78.34	(-220.97, 64.29)	0.2724	0.84	(0.49, 1.21)
Glucose ΔAUC(2h-5h)	Humalog		12	300.69					
(mg·h/dL)	LY900014		12	272.37	-28.32	(-136.21, 79.58)	0.5975	0.91	(0.47, 1.42)
Age group: Adolescents									
Glucose ΔAUC(0-30min)	Humalog		13	24.16					
(mg·h/dL)	LY900014		13	17.51	-6.65	(-11.62, -1.68)	0.0101	0.72	(0.55, 0.95)
Glucose ΔAUC(0-1h)	Humalog		13	81.08					
(mg·h/dL)	LY900014		13	66.63	-14.45	(-29.11, 0.21)	0.0532	0.82	(0.67, 0.98)
Glucose ΔAUC(0-2h)	Humalog		13	219.83					
(mg·h/dL)	LY900014		13	178.58	-41.25	(-84.56, 2.05)	0.0612	0.81	(0.63, 0.99)
Glucose ΔAUC(0-3h)	Humalog		13	377.48					
(mg·h/dL)	LY900014		13	305.22	-72.26	(-147.13, 2.60)	0.0581	0.81	(0.64, 0.97)
Glucose ΔAUC(0-4h)	Humalog		13	524.77					
(mg·h/dL)	LY900014		13	445.25	-79.52	(-185.03, 25.98)	0.1350	0.85	(0.70, 1.00)
Glucose ΔAUC(0-5h)	Humalog		13	646.55					
(mg·h/dL)	LY900014		13	585.17	-61.38	(-197.96, 75.20)	0.3678	0.91	(0.76, 1.05)

Parameter	Treatment		N	LS mean	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(2h-5h)	Humalog		13	426.72					
(mg·h/dL)	LY900014		13	406.60	-20.12	(-123.45, 83.20)	0.6949	0.95	(0.79, 1.13)
Age group: Adults									
Glucose ΔAUC(0-30min)	Humalog		14	21.06					
(mg·h/dL)	LY900014		14	16.66	-4.40	(-9.18, 0.38)	0.0703	0.79	(0.57, 1.06)
Glucose ΔAUC(0-1h)	Humalog		14	67.11					
(mg·h/dL)	LY900014		14	47.49	-19.62	(-33.73, -5.50)	0.0078	0.71	(0.53, 0.93)
Glucose ΔAUC(0-2h)	Humalog		14	145.54					
(mg·h/dL)	LY900014		14	112.54	-33.00	(-74.68, 8.69)	0.1171	0.77	(0.54, 1.13)
Glucose ΔAUC(0-3h)	Humalog		14	217.88					
(mg·h/dL)	LY900014		14	192.19	-25.69	(-97.76, 46.38)	0.4741	0.88	(0.61, 1.40)
Glucose ΔAUC(0-4h)	Humalog		14	284.52					
(mg·h/dL)	LY900014		14	277.27	-7.26	(-108.82, 94.31)	0.8855	0.97	(0.66, 1.63)
Glucose ΔAUC(0-5h)	Humalog		14	350.71					
(mg·h/dL)	LY900014		14	372.22	21.51	(-109.98, 152.99)	0.7418	1.06	(0.72, 1.82)
Glucose ΔAUC(2h-5h)	Humalog		14	205.17					
(mg·h/dL)	LY900014		14	259.68	54.50	(-44.96, 153.97)	0.2735	1.27	(0.81, 2.81)

Abbreviations: Δ = Change from Baseline; AUC(0-30min) = Area under the concentration-vs time curve from time zero to 30 minutes postdose; AUC(0-1h) = Area under the concentration-vs time curve from time zero to 1 hour postdose; AUC(0-2h) = Area under the concentration-vs time curve from time zero to 2 hours postdose; AUC(0-3h) = Area under the concentration-vs time curve from time zero to 3 hours postdose; AUC(0-4h) = Area under the concentration-vs time curve from time zero to 4 hours postdose; AUC(0-5h) = Area under the concentration-vs time curve from time zero to 5 hours postdose; AUC(2h-5h) = Area under the concentration-vs time curve from time 2 to 5 hours postdose; CI = Confidence interval; LS = Least squares; N = Number of patients; Δ = Change from Baseline;; LS = Least squares; N = Number of patients

Model: GD = Age Group + Period + Treatment + Sequence + Age Group*Treatment + 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

Table ITSA.7.11. **Summary of Key Change from Baseline in Glucodynamic Parameters (Arithmetic Mean [Standard Deviation]) Following Administration of Humalog and LY900014 in Children, Adolescents, and Adults with Type 1 Diabetes (Excluding Data after Any Treatment Intervention) - Part B**

	Arithmetic Mean (Standard Deviation)					
	Children		Adolescents		Adults	
PK Parameters	Humalog	LY900014	Humalog	LY900014	Humalog	LY900014
N	10	10	13	13	12	12
Mean Dose (U)	7.04	7.05	12.6	12.6	14.7	14.7
ΔBG_{max} (mg/dL)	176 (45.4)	171 (51.4)	181 (40.5)	191 (40.3)	136 (37.2)	133 (39.5)
ΔBG_{1h} (mg/dL)	112 (40.7)	110 (41.8)	120 (27.5)	121 (39.3)	85.0 (25.6)	73.6 (29.0)
ΔBG_{2h} (mg/dL)	120 (73.4)	135 (49.2)	141 [a] (34.8)	148 (53.3)	77.5 (54.7)	66.5 (51.5)
BG∆AUC(0-30min) (mg•h/dL)	17.2 (7.38)	18.7 (11.6)	24.8 (8.38)	19.7 (5.11)	15.9 (5.69)	14.9 (5.70)
BG∆AUC(0-1h) (mg•h/dL)	64.1 (20.4)	68.6 (29.4)	80.5 (19.7)	74.3 (18.6)	56.8 (14.4)	52.4 (16.7)
BG∆AUC(0-2h) (mg•h/dL)	175 (73.7)	188 (70.6)	206 [a] (35.6)	208 (60.0)	139 (47.3)	123 (56.6)
BG∆AUC(0-3h) (mg•h/dL)	248 [b] (125)	308 [c] (99.7)	351 [a] (68.3)	345 [a] (78.3)	221 (103)	180 [d] (96.1)
BG∆AUC(0-4h) (mg•h/dL)	359 [b] (162)	425 [e] (142)	486 [a] (115)	477 [a] (99.9)	287 [c] (144)	256 [d] (106)
BG∆AUC(0-5h) (mg•h/dL)	461 [b] (197)	508 [b] (174)	599 [a] (161)	586 [a] (128)	373 [c] (182)	345 [d] (125)
BG∆AUC(2-5h) (mg•h/dL)	316 [b] (169)	336 [b] (125)	394 [a] (132)	386 [a] (99.2)	245 [c] (139)	225 [d] (103)

Abbreviations: BG∆AUC(0-30min) = change from baseline glucose area under the concentration versus time curve from time zero to 30 minutes postmeal; BG∆AUC(0-1h) = change from baseline glucose area under the concentration versus time curve from time zero to 1 hour postmeal; BG∆AUC(0-2h) = change from baseline glucose area under the concentration versus time curve from time zero to 2 hours postmeal; BG∆AUC(0-3h) = change from baseline glucose area under the concentration versus time curve from time zero to 3 hours postmeal; BG∆AUC(0-4h) = change from baseline glucose area under the concentration versus time curve from time zero to 4 hours postmeal; BG∆AUC(0-5h) = change from baseline glucose area under the concentration versus time curve from time zero to 5 hours postmeal; BG∆AUC(2-5h) = change from baseline glucose area under the concentration versus time curve from time 2 to 5 hours postmeal; ΔBG_{1h} = change from baseline glucose at 1 hour; ΔBG_{2h} = change from baseline glucose at 2 hours; ΔBG_{max} = maximum change from baseline glucose value; N = number of patients; SD = standard deviation.

a N = 12.

b N = 7.

c N = 9.

d N = 10.

e N = 8.

Table ITSA.7.12. Summary of Key Change from Baseline in Glucodynamic Parameters (Arithmetic Mean [Standard Deviation]) Following Administration of Humalog and LY900014 in Children, Adolescents, and Adults with Type 1 Diabetes (LOCF) - Part B

	Arithmetic Mean (Standard Deviation)					
	Children		Adolescents		Adults	
PK Parameters	**Humalog**	**LY900014**	**Humalog**	**LY900014**	**Humalog**	**LY900014**
N	10	10	13	13	12	12
Mean Dose (U)	7.04	7.05	12.6	12.6	14.7	14.7
BG∆AUC(0-30min) (mg•h/dL)	17.2 (7.38)	18.7 (11.6)	24.8 (8.38)	19.7 (5.11)	15.9 (5.69)	14.9 (5.70)
BG∆AUC(0-1h) (mg•h/dL)	64.1 (20.4)	68.6 (29.4)	80.5 (19.7)	74.3 (18.6)	56.8 (14.4)	52.4 (16.7)
BG∆AUC(0-2h) (mg•h/dL)	175 (73.7)	188 (70.6)	211 (39.8)	208 (60.0)	139 (47.3)	123 (56.6)
BG∆AUC(0-3h) (mg•h/dL)	308 (141)	331 (119)	359 (70.9)	359 (89.6)	221 (103)	186 (101)
BG∆AUC(0-4h) (mg•h/dL)	448 (196)	473 (168)	496 (116)	497 (120)	310 (170)	258 (142)
BG∆AUC(0-5h) (mg•h/dL)	582 (254)	602 (221)	614 (163)	614 (160)	401 (235)	343 (194)
BG∆AUC(2-5h) (mg•h/dL)	407 (203)	414 (167)	402 (130)	406 (120)	262 (201)	220 (177)

Abbreviations: BG∆AUC(0-30min) = change from baseline glucose area under the concentration versus time curve from time zero to 30 minutes postmeal; BG∆AUC(0-1h) = change from baseline glucose area under the concentration versus time curve from time zero to 1 hour postmeal; BG∆AUC(0-2h) = change from baseline glucose area under the concentration versus time curve from time zero to 2 hours postmeal; BG∆AUC(0-3h) = change from baseline glucose area under the concentration versus time curve from time zero to 3 hours postmeal; BG∆AUC(0-4h) = change from baseline glucose area under the concentration versus time curve from time zero to 4 hours postmeal; BG∆AUC(0-5h) = change from baseline glucose area under the concentration versus time curve from time zero to 5 hours postmeal; BG∆AUC(2-5h) = change from baseline glucose area under the concentration versus time curve from time 2 to 5 hours postmeal; LOCF = last observation carried forward; N = number of patients; SD = standard deviation.

Table ITSA.7.13. Statistical Analysis of the Glucodynamic Parameters for Study I8B-MC-ITSA - Part B

Parameter	Treatment	N	LS mean	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)
Age group: Children								
Glucose ΔAUC(0-30min) (mg·h/dL)	Humalog	10	17.24					
	LY900014	10	18.76	1.52	(-4.37, 7.42)	0.6020	1.09	(0.67, 1.54)
Glucose ΔAUC(0-1h) (mg·h/dL)	Humalog	10	64.60					
	LY900014	10	68.58	3.98	(-11.20, 19.17)	0.5963	1.06	(0.77, 1.40)
Glucose ΔAUC(0-2h) (mg·h/dL)	Humalog	10	177.60					
	LY900014	10	186.62	9.02	(-29.28, 47.32)	0.6338	1.05	(0.78, 1.47)
Glucose ΔAUC(0-3h) (mg·h/dL)	Humalog	7	247.46					
	LY900014	9	305.60	58.14	(-8.59, 124.87)	0.0850	1.23	(0.95, 1.62)
Glucose ΔAUC(0-4h) (mg·h/dL)	Humalog	7	358.37					
	LY900014	8	425.47	67.10	(-6.17, 140.37)	0.0710	1.19	(0.89, 1.52)
Glucose ΔAUC(0-5h) (mg·h/dL)	Humalog	7	447.77					
	LY900014	7	506.46	58.69	(-35.75, 153.14)	0.2120	1.13	(0.80, 1.47)
Glucose ΔAUC(2h-5h) (mg·h/dL)	Humalog	7	306.15					
	LY900014	7	334.22	28.07	(-47.39, 103.52)	0.4504	1.09	(0.78, 1.49)
ΔBGmax (mg/dL)	Humalog	10	176.83					
	LY900014	10	169.69	-7.13	(-30.52, 16.25)	0.5383	0.96	(0.82, 1.12)
ΔBG1h (mg/dL)	Humalog	10	113.28					
	LY900014	10	108.86	-4.42	(-24.41, 15.57)	0.6553	0.96	(0.76, 1.22)
ΔBG2h (mg/dL)	Humalog	10	122.06					
	LY900014	10	133.31	11.25	(-19.69, 42.18)	0.4631	1.09	(0.81, 1.78)
Age group: Adolescents								
Glucose ΔAUC(0-30min) (mg·h/dL)	Humalog	13	24.74					
	LY900014	13	19.70	-5.04	(-10.18, 0.11)	0.0546	0.80	(0.64, 1.01)
Glucose ΔAUC(0-1h) (mg·h/dL)	Humalog	13	80.25					
	LY900014	13	74.31	-5.94	(-19.19, 7.32)	0.3680	0.93	(0.78, 1.09)
Glucose ΔAUC(0-2h) (mg·h/dL)	Humalog	12	209.82					
	LY900014	13	208.72	-1.09	(-35.52, 33.33)	0.9487	0.99	(0.82, 1.17)
Glucose ΔAUC(0-3h) (mg·h/dL)	Humalog	12	350.97					
	LY900014	12	345.20	-5.77	(-57.96, -46.43)	0.8217	0.98	(0.86, 1.12)

Parameter	Treatment	N	LS mean	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(0-4h) (mg·h/dL)	Humalog	12	486.03					
	LY900014	12	476.85	-9.18	(-65.59, 47.22)	0.7399	0.98	(0.88, 1.10)
Glucose ΔAUC(0-5h) (mg·h/dL)	Humalog	12	599.22					
	LY900014	12	585.84	-13.38	(-85.33, 58.57)	0.7047	0.98	(0.87, 1.11)
Glucose ΔAUC(2h-5h) (mg·h/dL)	Humalog	12	393.54					
	LY900014	12	385.64	-7.90	(-65.38, 49.58)	0.7792	0.98	(0.84, 1.17)
ΔBGmax (mg/dL)	Humalog	13	180.25					
	LY900014	13	191.54	11.30	(-9.12, 31.71)	0.2678	1.06	(0.94, 1.21)
ΔBG1h (mg/dL)	Humalog	13	119.18					
	LY900014	13	121.01	1.83	(-15.61, 19.28)	0.8316	1.02	(0.86, 1.16)
ΔBG2h (mg/dL)	Humalog	12	146.67					
	LY900014	13	148.14	1.46	(-26.41, 29.34)	0.9153	1.01	(0.78, 1.27)
Age group: Adults								
Glucose ΔAUC(0-30min) (mg·h/dL)	Humalog	12	15.86					
	LY900014	12	14.82	-1.05	(-6.42, 4.33)	0.6943	0.93	(0.64, 1.38)
Glucose ΔAUC(0-1h) (mg·h/dL)	Humalog	12	56.35					
	LY900014	12	52.47	-3.88	(-17.73, 9.96)	0.5715	0.93	(0.70, 1.23)
Glucose ΔAUC(0-2h) (mg·h/dL)	Humalog	12	136.36					
	LY900014	12	124.62	-11.74	(-46.67, 23.18)	0.4972	0.91	(0.67, 1.19)
Glucose ΔAUC(0-3h) (mg·h/dL)	Humalog	12	214.03					
	LY900014	10	186.78	-27.25	(-83.70, 29.19)	0.3303	0.87	(0.61, 1.25)
Glucose ΔAUC(0-4h) (mg·h/dL)	Humalog	9	275.05					
	LY900014	10	257.56	-17.49	(-82.27, 47.29)	0.5831	0.94	(0.74, 1.15)
Glucose ΔAUC(0-5h) (mg·h/dL)	Humalog	9	360.79					
	LY900014	10	343.85	-16.94	(-99.56, 65.69)	0.6765	0.95	(0.79, 1.14)
Glucose ΔAUC(2h-5h) (mg·h/dL)	Humalog	9	237.12					
	LY900014	10	222.24	-14.88	(-80.89, 51.14)	0.6465	0.94	(0.71, 1.19)
ΔBGmax (mg/dL)	Humalog	12	135.31					
	LY900014	12	134.74	-0.57	(-21.90, 20.76)	0.9568	1.00	(0.82, 1.19)
ΔBG1h (mg/dL)	Humalog	12	84.08					
	LY900014	12	74.48	-9.60	(-27.83, 8.63)	0.2910	0.89	(0.67, 1.14)

Parameter	Treatment	N	LS mean	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)
ΔBG2h (mg/dL)	Humalog	12	75.56					
	LY900014	12	67.82	-7.74	(-35.95, 20.47)	0.5791	0.90	(0.58, 1.29)

Abbreviations: Δ = Change from Baseline; AUC(0-30min) = Area under the concentration-vs time curve from time zero to 30 minutes postdose; AUC(0-1h) = Area under the concentration-vs time curve from time zero to 1 hour postdose; AUC(0-2h) = Area under the concentration-vs time curve from time zero to 2 hours postdose; AUC(0-3h) = Area under the concentration-vs time curve from time zero to 3 hours postdose; AUC(0-4h) = Area under the concentration-vs time curve from time zero to 4 hours postdose; AUC(0-5h) = Area under the concentration-vs time curve from time zero to 5 hours postdose; AUC(2h-5h) = Area under the concentration-vs time curve from time 2 to 5 hours postdose; BGmax = maximum raw glucose value; BG1h = raw glucose at 1hr; BG2h = raw glucose at 2hr CI = Confidence interval; LS = Least squares; N = Number of patients

Model: GD = Age Group + Period + Treatment + Sequence + Age Group*Treatment + 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

4.3 Pharmacometrics Review

4.3.1. Review Summary

Eli Lilly and Company submitted an efficacy supplement seeking regulatory approval of Lyumjev (LY900014, insulin lispro-aabc 100 units/mL) for expanding the indication to pediatric patients with diabetes mellitus and adding continuous subcutaneous insulin infusion (CSII) as a condition of use in the pediatric population. This submission includes new clinical data from Phase 1 study I8B-MC-ITSA (ITSA) and Phase 3 study I8B-MC-ITSB (ITSB), and two pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation reports (multiple daily injection (MDI) pediatric/adult population PK/PD report and CSII pediatric/adult PK/PD population report).

The applicant conducted Population PK (PopPK) analysis using data from Study ITSA to characterize the observed serum insulin lispro following MDI or CSII of LY900014 or Humalog in type 1 diabetes mellitus (T1DM) patients. In general, the applicant's PopPK model appears adequate to describe the observed serum insulin lispro profile in children, adolescents and adults after optimization based on reviewer's suggestions. Therefore, the final adult/pediatric PopPK model is acceptable to simulate serum insulin lispro concentrations for Exposure-Response (E-R) analyses for efficacy and safety measurements.

The applicant's Integrated Glucose Insulin (IGI) model developed for patients with T1DM generally captured the mean trend of glucose dynamics following MDI and CSII administration of LY900014 and Humalog for children, adolescents and adults in Study ITSA after optimization based on reviewer's suggestions. This model was utilized to characterize the E-R relationship between insulin lispro concentrations and postprandial glucose (PPG) lowering following SC administration of either LY900014 or Humalog in pediatric patients with T1DM via MDI and CSII therapy.

Finally, PopPK and PK/PD models were used to predict the PK of insulin lispro and PPG response following SC injection of either LY900014 or Humalog in pediatric patients with type 2 diabetes mellitus (T2DM), and in T1DM patients given 20 minutes after the start of the meal. The results showed that the model-predicted insulin lispro PK in children and adolescents with T2DM showed an accelerated absorption and a reduction in the late insulin exposure with LY900014 compared to Humalog as observed in adults with T2DM. When both insulins (LY900014 and Humalog) were given prior to the start of the meal or 20 minutes after the start of the meal, the model-predicted glucose profiles show a greater glucose-lowering effect with LY900014 than Humalog in children, adolescents, and adults with T2DM. In addition, LY900014 and Humalog showed comparable hypoglycemia risks (≤ 70 mg/dL and ≤ 54 mg/dL) for all three age groups (children, adolescents, and adults) via either MDI or CSII therapy. Simulation showed that younger children (≤ 26 kg down to 4 years of age) did not have increased hypoglycemia risks as compared to older children (> 26 kg).

In general, data from Study ITSA, PopPK and PK/PD analyses confirmed that the differences in the time course of insulin lispro concentration for LY900014 and Humalog described the differences in the observed PPG response in pediatric patients with T1D on MDI and CSII therapy. In addition, the PK/PD model confirmed that the same PK/PD relationship remained, independent of adult or pediatric patients with T1DM or whether LY900014 and Humalog was administered as MDI or CSII therapy. The PopPK and PK/PD analyses provided supporting evidence for extrapolating the indication from prior to the start of the meal to 20 minutes after the start of the meal, and from T1DM patients to T2DM patients in children, adolescents and adults.

4.3.2. Population PK and PD/PD Analysis

4.3.2.1. Population PK Analysis

4.3.2.1.1 Applicant's Population PK Analysis

Objectives

The objectives of the applicant's Population PK analysis were to

- characterize the pharmacokinetics (PK) of insulin lispro following subcutaneous (SC) administration of either LY900014 or Humalog in pediatric patients with T1DM via MDI therapy
- characterize the PK of insulin lispro following SC infusion of either LY900014 or Humalog in pediatric patients with T1DM via CSII therapy
- predict the PK of insulin lispro following SC injection of either LY900014 or Humalog in pediatric patients with T2DM

Data

The PopPK analyses were based on PK data from Study ITSA. For Part A for MDI therapy, the NONMEN PK dataset included 1428 observed serum insulin lispro concentration data from 42 patients with T1DM including 13 children (6 to <12 years), 14 adolescents (12 to <18 years), and 15 adults (18 to <65 years). For Part B for CSII therapy, the NONMEN PK dataset contained 1296 observations from 37 participants, including 12 children, 13 adolescents and 12 adults. The study design, study population, and timing of blood samples of Study ITSA are presented in **Table 1**.

Table 2. Subject Demographics (Median [Range]) and Other Baseline Characteristics in Part A and Part B of Study ITSA

Part A

Age range (years)	N	Age (years)	Body weight (kg)	Race N (%)	Sex N (%)	
					Male	Female
6 to <12	13	9 (8-11)	33.5 (25.1-49.8)	White 12 (92) Multiple 1 (8)	4 (31)	9 (69)
12 to <18	14	14 (12-16)	60.9 (45.2-84.9)	White 13 (93) Multiple 1 (7)	9 (64)	5 (36)
18 to <65	15	28 (18-58)	78.3 (56.5-90.8)	White 12 (80) Asian 1 (7) Black or African American 1 (7) Multiple 1 (7)	9 (60)	6 (40)

Part B

Age range (yr)	N	Age (yr)	Body Weight (kg)	Race N (%)	Sex N (%)	
					Male	Female
6 to <12	12	9 (8-11)	36.0 (25.6–41.5)	White 11 (92) Multiple 1 (8)	2 (17)	10 (83)
12 to <18	13	15 (12-17)	61.5 (45.8-78.1)	White 12 (92) Multiple 1 (8)	10 (77)	3 (23)
18 to <65	12	27 (20-57)	73.2 (55.6-88.1)	White 10 (83) Asian 2 (17)	5 (42)	7 (58)

Abbreviations: N=Number of subjects
Source: Applicant's Population MDI and CSII PK/PD reports. Table 7.5.

provides summary statistics of the baseline demographic covariates in the analysis datasets.

Table 1. Summary of Studies with PK Sampling Included in Population PK Analysis.

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject	Dose(s) [mg]

ITSA	This was a multi-center, Phase 1, randomised, 2-part, patient- and investigator-blind, 2-period crossover study in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years) with T1DM currently using an MDI regimen (Part A) and CSII pump (Part B). **PK sampling:** 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 90, 120, 150, 180, 240, 300, 360, and 420 minutes postdose. **Blood Glucose Sampling:** -30, -15, 0 (premeal), 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300 minutes postmeal	Part A: N = 42 Subject: Patients with T1DM Part B: N = 37 Subject: Patients with T1DM	0.2 U/kg LY900014 (final commercial formulation) 0.2 U/kg Humalog Part A: MDI regimen Part B: CSII pump

[*] *Source: Applicant's Study ITSA report.*

Table 2. Subject Demographics (Median [Range]) and Other Baseline Characteristics in Part A and Part B of Study ITSA

Part A

Age range (years)	N	Age (years)	Body weight (kg)	Race N (%)	Sex N (%)	
					Male	Female
6 to <12	13	9 (8-11)	33.5 (25.1-49.8)	White 12 (92) Multiple 1 (8)	4 (31)	9 (69)
12 to <18	14	14 (12-16)	60.9 (45.2-84.9)	White 13 (93) Multiple 1 (7)	9 (64)	5 (36)
18 to <65	15	28 (18-58)	78.3 (56.5-90.8)	White 12 (80) Asian 1 (7) Black or African American 1 (7) Multiple 1 (7)	9 (60)	6 (40)

Part B

Age range (yr)	N	Age (yr)	Body Weight (kg)	Race N (%)	Sex N (%)	
					Male	Female
6 to <12	12	9 (8-11)	36.0 (25.6–41.5)	White 11 (92) Multiple 1 (8)	2 (17)	10 (83)
12 to <18	13	15 (12-17)	61.5 (45.8-78.1)	White 12 (92) Multiple 1 (8)	10 (77)	3 (23)
18 to <65	12	27 (20-57)	73.2 (55.6-88.1)	White 10 (83) Asian 2 (17)	5 (42)	7 (58)

Abbreviations: N=Number of subjects

Source: Applicant's Population MDI and CSII PK/PD reports. Table 7.5.

<u>Methods</u>

Nonlinear mixed effect modeling was conducted using NONMEM (version 7.4.2). The First-order conditional estimation with interaction (FOCEI) method was used to estimate the model parameters.

MDI PopPK model

- *Final Adult Insulin Lispro Model*

The PK of insulin lispro following administration of LY900014 and Humalog during MDI therapy for adults was best described using a 3-compartment disposition model with linear elimination and combined zero- and first-order absorption (**Figure 1**). This model was generally acceptable according to the pharmacometrics review on LY900014 via SC or IV routes (refer to BLA 761109 Insulin lispro OCP review by Dr. Sista and Dr. Li darrts on 05/06/2020).

- *Optimization of the Final Adult Insulin Lispro PopPK Model for Children, Adolescents, and Adults with T1DM*

The Applicant further optimized the final adult insulin lispro MDI PopPK model for children, adolescents, and adults based on data from Study ITSA.

First, the differences between adult healthy subject's estimates and those for the patients with T1DM (children, adolescents, and adults) in Study ITSA were estimated for the previously identified population covariates: SC bioavailability, zero-order duration of absorption, first-order absorption rate, and central volume of distribution. Secondly, the difference between the first-order absorption of LY900014 and Humalog was estimated. Lastly, the allometric scaling coefficients for clearance and volume parameters were estimated.

Goodness-of-fit was evaluated using changes in the NONMEM objective function and simulation-based diagnostics (VPCs) to evaluate the predictive performance of the model over the full-time course of the PK profile.

CSII PopPK Model

- *Adult Insulin Lispro CSII Model Development*

The same structural PK model developed for MDI therapy was applied to the CSII therapy, and this PopPK has been reviewed previous and is considered acceptable (refer to BLA 761109 Insulin lispro OCP supplement review by Dr. Samant and Liu darrts on 07/06/2021).

- *Optimization of the Adult Insulin Lispro CSII Model for Children, Adolescents, and Adults with T1DM (Study ITSA)*

PK parameters for SC bioavailability, zero-order duration of absorption, first-order absorption rate, fraction absorbed via transit compartments, mean transit time, and central volume of distribution were estimated for children, adolescents, and adults with T1DM via CSII therapy in

Study ITSA (Part B). The allometric scaling coefficients for clearance and volume parameters were estimated.

Goodness-of-fit was evaluated using changes in the NONMEM objective function and simulation-based diagnostics (VPCs) to evaluate the predictive performance of the model over the full-time course of the PK profile.

Simulations

- *Prediction of Insulin Lispro Concentrations Following LY900014 and Humalog in Children, Adolescents and Adults with T2DM*

PK of LY900014 has not been studied in pediatric patients with T2DM in either Studies ITSA or ITSB. Therefore, in order to understand the PK characteristics of insulin lispro following LY900014 and Humalog in pediatric T2DM patients, the PK model developed with Phase 1 data for children, adolescents, and adults with T1DM was used to simulate the insulin lispro concentrations following a SC injection of a 0.2 U/kg dose of either LY900014 or Humalog in children, adolescents, and adults with T2DM following MDI therapy.

The population covariates for pediatric patients with T2DM were adjusted based on the final adult PopPK model for healthy subjects, T1DM and T2DM. Additionally, the allometric scaling coefficients for clearance and volume parameters estimated in the optimized PK model for T1DM children, adolescents, and adults were used in the simulation for children, adolescents, and adults with T2DM.

Table 3. Differences between Healthy Subjects Versus Adult Patients with T1DM or T2DM

Covariate	PK Attribute	PK Parameters	Median (95% CI) Change in PK Parameters[a]
Differences between healthy subjects and patients with T1DM or T2DM	Bioavailability	SC bioavailability relative to IV LY900014 in HS (BIO)	22% (17% – 30%) lower in T1DM compared to HS
			Similar for T2DM and HS
	Absorption rate	Rate of absorption via transit compartment compared to HS (k_a)	118% (83% – 176%) faster in T1DM
			74% (31% – 130%) faster in T2DM
		Duration of zero-order absorption compared to HS (DUR)	30% (15% – 52%) longer in T1DM
			39% (26% – 73%) longer in T2DM
	Volume of distribution	Central volume of distribution for SC administration compared to HS (V2_SC)	31% (12% – 57%) increase in T1DM
			93% (62% – 132%) increase in T2DM

Abbreviations: CI = confidence interval; HS = healthy subjects; IV = intravenous; PK = pharmacokinetics; SC = subcutaneous; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

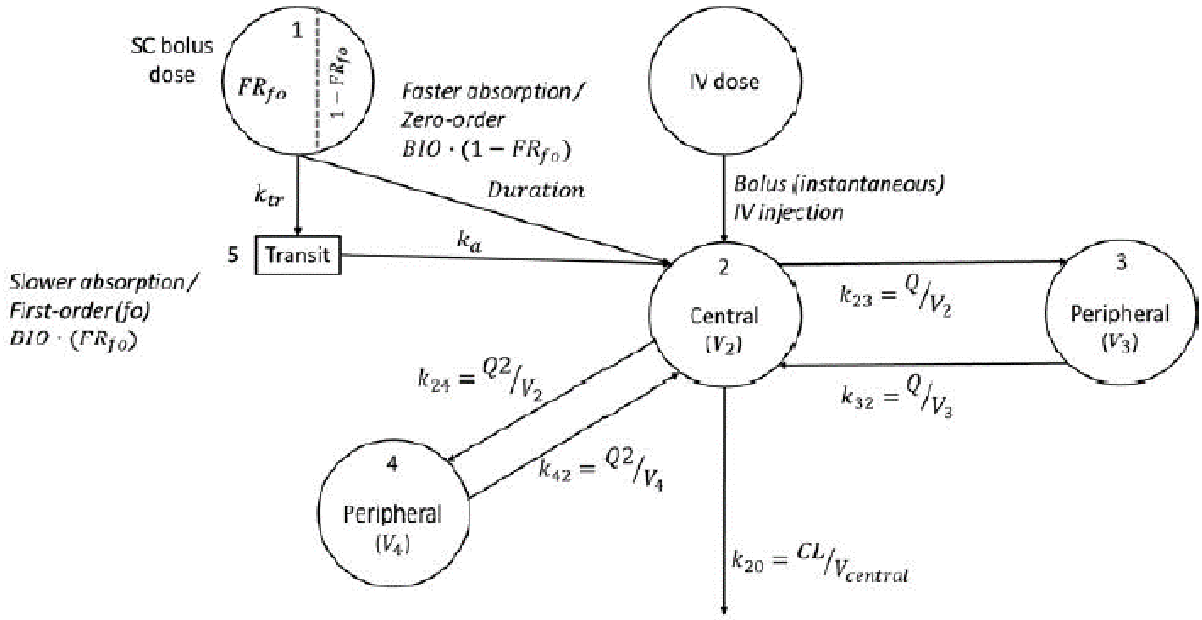
[a] Median and 95% CI based on bootstrap evaluation.

Source: Applicant's population PK/PD report. Table 8.1.

Reviewer's Comments:

The proposed approach to simulate PK of insulin lispro in pediatric and adult patients are acceptable. The acceptability of PopPK model and simulations are discussed in the following sections.

Figure 1. Insulin Lispro IV and SC Structural PopPK Model following LYUMJEV or Humalog Administration



Source: Applicant's population PK/PD report.

<u>Results</u>

Applicant's Final Model

- *Optimized Pediatric/Adult MDI PopPK Model*

The parameter estimates for Applicant's final MDI population PK model for pediatric and adult are listed in **Table 4**. The Visual Predictive Check (VPC) plots for the final covariate model with all data are shown in **Figure 2**.

Table 4. Parameter Estimates (RSE) and Median (95% CI) for the Applicant's Final MDI Model for children, adolescents and adults with T1DM

		Adult PK Model				**Study ITSA (Part A): Children, Adolescents, and Adults with T1DM**				
Parameter		**Estimate (%RSE)**		**% Variability (%RSE)**		**Estimate (%RSE)**		**% Variability (%RSE)**	**Bootstrap (N=400)**	
									Median	**95% CI**
Clearance (CL) (L/h)	Θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.6 *fix*[b]	Θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.6 *fix*[b]	28.6 *fix*[a]	28.6 *fix*[c]
Central volume IV (V2_IV) (L)	Θ_2	4.73 *fix*[a]	$\omega_{2,2}$	6.25 *fix*[a]	Θ_2	4.73 *fix*[a]	$\omega_{2,2}$	6.25 *fix*[a]	4.73 *fix*[c]	4.73 *fix*[c]
Central volume SC (V2_SC) (L)	Θ_9	17.4 *fix*[c]	$\omega_{5,5}$	43.0 *fix*[c]	Θ_9	17.4 *fix*[c]	$\omega_{5,5}$	43.0 *fix*[c]	17.4 *fix*[c]	17.4 *fix*[c]
Intercompartmental clearance 1 (Q) (L/h)	Θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.8 *fix*[a]	Θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.8 *fix*[a]	3.89 *fix*[c]	3.89 *fix*[c]
Peripheral volume 1 (V3) (L)	Θ_4	1.49 *fix*[a]	$\omega_{7,7}$	24.6 *fix*[a]	Θ_4	1.49 *fix*[a]	$\omega_{7,7}$	24.6 *fix*[a]	1.49 *fix*[c]	1.49 *fix*[c]
Fraction absorbed via transit compartments (FR_{fo})	Θ_5	0.872 *fix*[b]	$\omega_{9,9}$	0 *fix*	Θ_5	0.872 *fix*[b]	$\omega_{9,9}$	0 *fix*	0.872 *fix*[c]	0.872 *fix*[c]
Mean transit time (MTT) (h)	Θ_6	1.18 *fix*[c]	$\omega_{3,3}$	50 *fix*[c]	Θ_6	1.18 *fix*[c]	$\omega_{3,3}$	50 *fix*[c]	1.18 *fix*[c]	1.18 *fix*[c]
Duration of zero-order absorption (DUR) (h)	Θ_7	0.239 *fix*[c]	$\omega_{4,4}$	42.2 *fix*[c]	Θ_7	0.239 *fix*[c]	$\omega_{4,4}$	42.2 *fix*[c]	0.239 *fix*[c]	0.239 *fix*[c]
Bioavailability (BIO)	Θ_8	0.542 *fix*[c]	$\omega_{8,8}$	31.4 *fix*[c]	Θ_8	0.542 *fix*[c]	$\omega_{8,8}$	31.4 *fix*[c]	0.542 *fix*[c]	0.542 *fix*[c]
First-order absorption rate constant (K_a) (h^{-1})	Θ_{10}	2.63 *fix*[c]	$\omega_{10,10}$	78.7 *fix*[c]	Θ_{10}	2.63 *fix*[c]	$\omega_{10,10}$	78.7 *fix*[c]	2.63 *fix*[c]	2.63 *fix*[c]
Intercompartmental clearance 2 (Q2) (L/h)	Θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	Θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	1.73 *fix*[c]	1.73 *fix*[c]
Peripheral volume 2 (V4) (L)	Θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	Θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	2.0 *fix*[c]	2.0 *fix*[c]
Differences in Humalog® relative to LY900014										
Fraction absorbed via transit compartments	Θ_{13}	0.14 *fix*[b]		N/A	Θ_{13}	0.14 *fix*[b]		N/A	0.14 *fix*[c]	0.14 *fix*[c]
First-order absorption rate constant (K_a) (h^{-1}) for Humalog	Θ_{14}	-0.597 *fix*[c]		N/A	Θ_{14}	-0.774 (7.8)		N/A	-0.772	-0.835- -0.564
Differences in T1DM relative to healthy subjects										
Bioavailability for T1DM	Θ_{15}	-0.222 *fix*[c]		N/A	Θ_{15}	-0.39 (57)		N/A	-0.391	-0.436- -0.351
First-order absorption rate constant for T1DM (K_a) (h^{-1})	Θ_{17}	1.15 *fix*[c]		N/A	Θ_{17}	3.58 (0.2)		N/A	3.56	1.16-4.90
Central volume SC for T1DM (L)	Θ_{19}	0.302 *fix*[c]		N/A	Θ_{19}	0.179 (1.6)		N/A	0.171	-0.025- 0.373
Duration of zero-order absorption T1DM (h)	Θ_{21}	0.296 *fix*[c]		N/A	Θ_{21}	3.88 (0)		N/A	3.71	2.92-4.68
Allometric coefficient for bodyweight effect										
Clearance		0.75 *fix*[c]		N/A	Θ_{23}	0.553		N/A	0.567	0.411- 0.732
Central volume		1.0 *fix*[c]		N/A	Θ_{24}	1.06		N/A	1.07	0.573-1.62
Proportional error (%)	$\delta_{1,1}$	34 (1.1)		N/A	$\delta_{1,1}$	35 (0)		N/A	35	31-39

CI = confidence interval; HV = healthy volunteers; IV = intravenous administration route; N =number; %RSE = relative standard error of the estimate as a percentage; PK = pharmacokinetics; N/A = not applicable; SC = subcutaneous administration route; T1DM = type 1 diabetes mellitus; T2DM =type 2 diabetes mellitus.

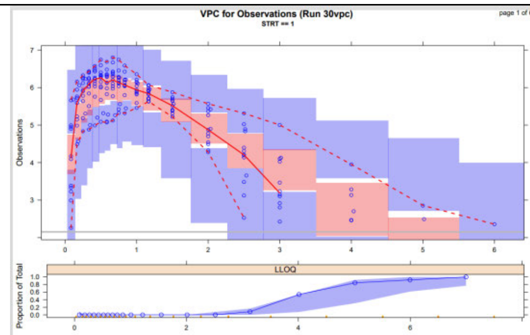
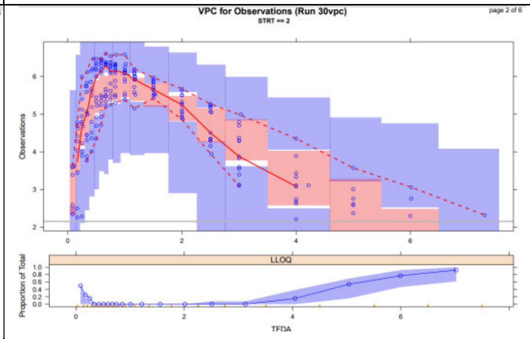
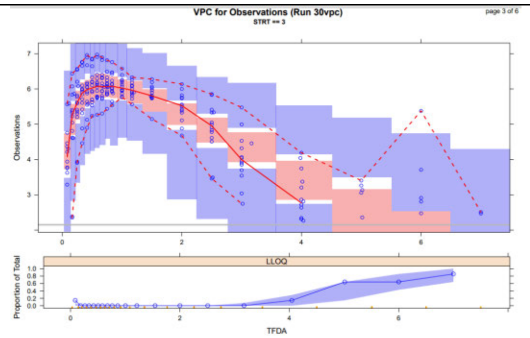
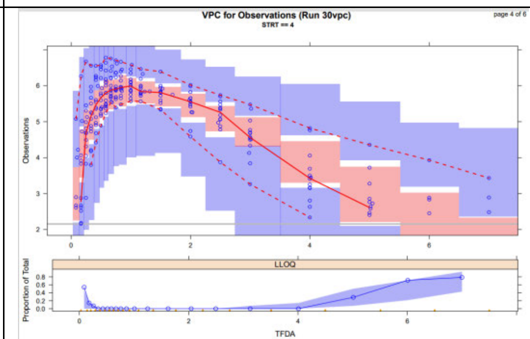
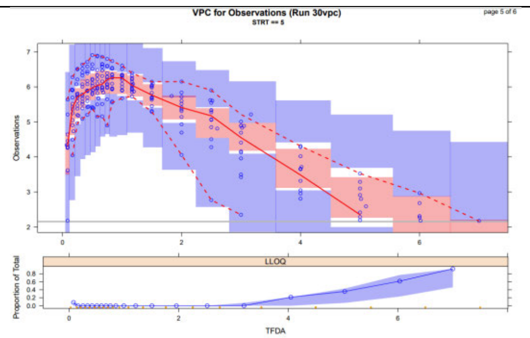
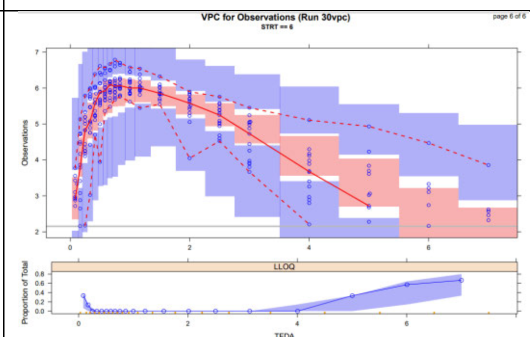
[a] Parameter values were fixed to the estimates from the IV model for LY900014.

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

[c] Parameter values were fixed to the estimates from the Final Full IV+SC model for LY900014 and Humalog.

Source: Applicant's MDI population PK/PD report, Table 9.1.

Figure 2. Visual predictive checks of the model predictions of serum insulin lispro concentration following SC administration of a 0.2U/kg dose of LY900014 and Humalog via MDI dosing in children, adolescents and adults with T1DM.

	LY900014	Humalog
Children		
Adolescents		
Adults		

Note: The blue circles represent observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed red lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same.

Source: Applicant's PopPK/PD report. Figures 9.4 to 9.9

The Applicant concluded that the VPCs for LY900014 and Humalog in children, adolescents, and adults following MDI dosing showed good agreement between the median of the observed and the 95% CI around the median of the simulated data.

The Applicant concluded based on the 95% prediction interval (95% PI), the model also captured the interindividual variability observed in Study ITSA. These simulation-based diagnostics confirmed that estimating only the population differences was sufficient to describe both the LY900014 and Humalog data in Study ITSA. The differences between LY900014 and Humalog as estimated in adult subjects described the differences in pediatric patients with T1DM as well.

- *Optimized Pediatric/Adult CSII PopPK Model*

The parameter estimates for Applicant's final CSII PopPK model for pediatric and adult are listed in **Table 5**.

Table 5. Pharmacokinetic Parameters for Insulin Lispro CSII PopPK Model Following Subcutaneous Infusion of LY900014

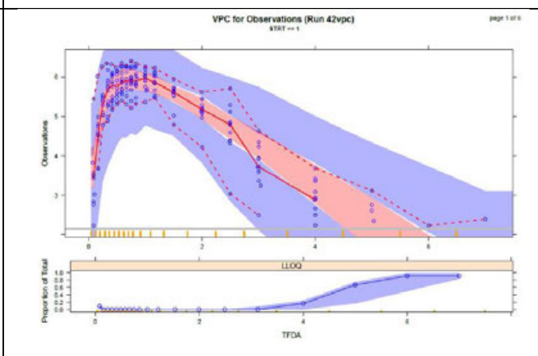
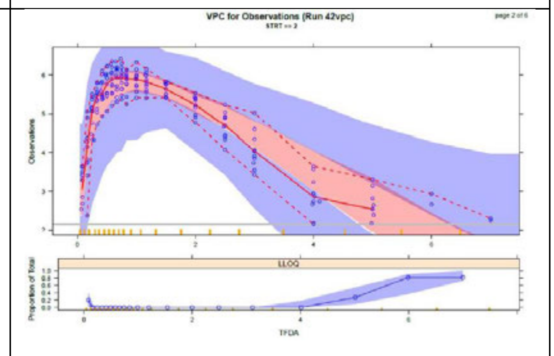
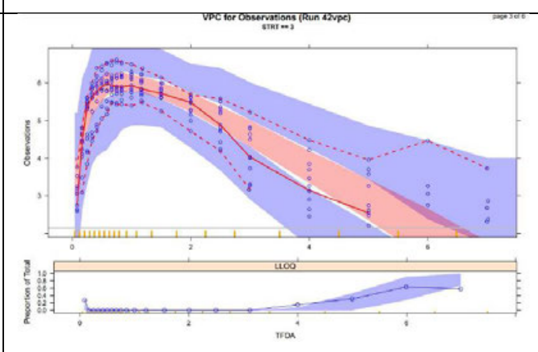
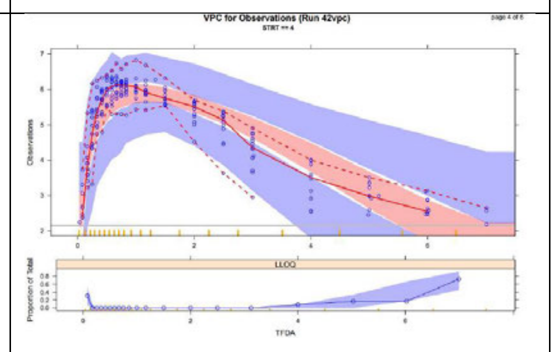
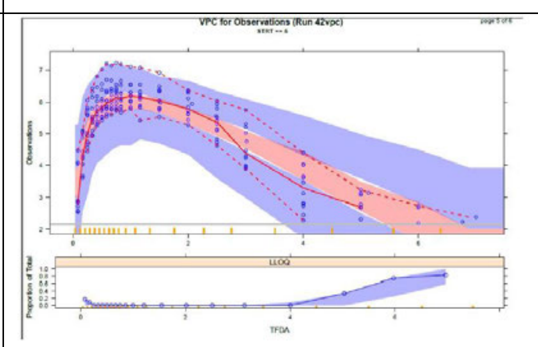
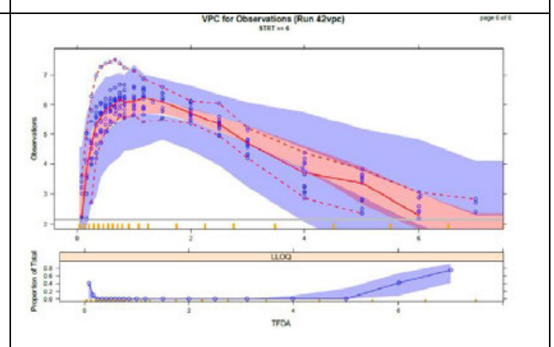
	Adult CSII PK Model						ITSA (Part B): Children, Adolescents, Adults				
Parameter		**Estimate (%RSE)**		**% Variability (%RSE)**[b]		**Bootstrap 95% CI**		**Estimate (%RSE)**	**% Variability (%RSE)**[b]	**Bootstrap Median**	**Bootstrap 95% CI**
Clearance (CL) (L/h)	θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.7 *fix*[a]	θ_1	N/A	θ_1	28.6 *fix*[a]	15.7 *fix*[a]	28.6 *fix*[a]	N/A
Central volume SC (V2) (L)	θ_9	3.27 (15.4)	$\omega_{5,5}$	146.9 (10.0)	θ_9	2.64, 4.1	θ_9	15.1 (0)	146.9 *fix*[b]	15.1	13.8, 16.4
Intercompartmental clearance 1 (Q) (L/h)	θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.9 *fix*[a]	θ_3	N/A	θ_3	3.89 *fix*[a]	14.9 *fix*[a]	3.89 *fix*[a]	N/A
Peripheral volume 1 (V3) (L)	θ_4	1.49 *fix*[a]	$\omega_{7,7}$	25.0 *fix*[a]	θ_4	N/A	θ_4	1.49 *fix*[a]	25.0 *fix*[a]	1.49 *fix*[a]	N/A
Intercompartmental clearance 2 (Q2) (L/h)	θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	θ_{11}	N/A	θ_{11}	1.73 *fix*[a]	12.5 *fix*[a]	1.73 *fix*[a]	N/A
Peripheral volume 2 (V4) (L)	θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	θ_{12}	N/A	θ_{12}	2.0 *fix*[a]	8.0 *fix*[a]	2.0 *fix*[a]	N/A
Fraction absorbed via transit compartments (FR_{tr})	θ_5	0.859 (1.2)	$\omega_{9,9}$	7.1 (15.6)	θ_5	0.826, 0.891	θ_5	0.972 (4.1)	7.1 *fix*[b]	0.972	0.963, 0.980
Mean transit time (MTT) (h)	θ_6	2.07 (4.5)	$\omega_{3,3}$	31.6 (21.8)	θ_6	1.9, 2.26	θ_6	1.67 (2.4)	31.6 *fix*[b]	1.67	1.54, 1.80
Duration of zero-order absorption (h)	θ_7	2.49 (1.3)	$\omega_{4,4}$	7.1 *fix*[a]	θ_7	2.39, 2.63	θ_7	0.548 (0)	7.1 *fix*[a]	0.548	0.503, 0.594
Bioavailability prandial insulin (BIO)	θ_8	0.423 (1.8)	$\omega_{8,8}$	16.6 (25.7)	θ_8	0.402, 0.443	θ_8	0.336 (0)	16.6 *fix*[b]	0.336	0.323, 0.348
First-order absorption rate constant (k_a) (h^{-1})											
LY900014 ITSC on Day 1 (SS)	θ_{10}	3.04 (11.1)	$\omega_{10,10}$	75.9 (11.6)	θ_{10}	2.05, 4.08	θ_{10}	3.7 (0)	75.9*fix*[b]	3.70	3.21, 4.19
Humalog ITSC on Day 1 (SS)	θ_{13}	1.79 (9.8)	$\omega_{16,16}$	68.3 (14.8)	θ_{13}	1.3, 2.38	θ_{13}	2.28 (0.1)	68.3fix[b]	2.28	1.84, 2.71
LY900014 ITSC on Day 3 (SS)	θ_{14}	6.57 (0.8)	$\omega_{17,17}$	4 (13.2)	θ_{14}	5.19, 7.35	θ_{14}	N/A	N/A	N/A	N/A
Humalog ITSC on Day 3 (SS)	θ_{15}	3.09 (6.2)	$\omega_{18,18}$	39.8 (31.6)	θ_{15}	2.46, 3.8	θ_{15}	N/A	N/A	N/A	N/A
LY900014 ITRF on Day 1 (RS)	θ_{19}	3.91 (7.9)	$\omega_{19,19}$	47.1 (22.5)	θ_{19}	3.15, 5.21	θ_{16}	N/A	N/A	N/A	N/A
Humalog ITRF on Day 1 (RS)	θ_{20}	2.29 (6.1)	$\omega_{20,20}$	37.4 (22.2)	θ_{20}	1.94, 2.71	θ_{17}	N/A	N/A	N/A	N/A
LY900014 ITRF on Day 3 (RS)	θ_{21}	19.1 (14.4)	$\omega_{21,21}$	110.3 (7.8)	θ_{21}	12.3, 55.6	θ_{18}	N/A	N/A	N/A	N/A
Humalog ITRF on Day 3 (RS)	θ_{22}	4.07 (6.9)	$\omega_{22,22}$	38.0 (22.3)	θ_{22}	3.31, 5.05	θ_{19}	N/A	N/A	N/A	N/A
Allometric coefficient for bodyweight effect											
Clearance		0.75 *fix*[c]		N/A	θ_{23}	N/A	θ_{20}	0.629 (0)	N/A	0.629	0.583, 0.674
Central volume		1.0 *fix*[c]		N/A	θ_{24}	N/A	θ_{21}	1.41 (0)	N/A	1.41	1.27, 1.55
Proportional error (%)	$\delta_{1,1}$	24.9 (2.2)[c]		N/A	$\delta_{1,1}$	23.4, 27.6		24.9 fix[b]	N/A	24.9 fix[b]	N/A

Abbreviations: CSII = continuous subcutaneous insulin infusion; IV = intravenous; N/A = not applicable; PK = pharmacokinetics; %RSE = relative standard error of the estimate as a percentage; RS = rapid speed; SC = subcutaneous; SS = standard speed; T1DM = type 1 diabetes mellitus.

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

[b] Parameter values were fixed to the adult pump PK model. [c] Parameter values were fixed to the estimates from the Final Full IV+SC model for LY900014 and Humalog.
Source: Applicant's CSII population PK/PD report, Table 9.1.

Figure 3. Visual predictive checks of the PopPK model predictions of serum insulin lispro concentration following SC infusion of a 0.2 U/kg dose of LY900014 vis CSII infusion in children, adolescents and adults with T1DM.

	LY900014	Humalog
Children		
Adolescents		
Adults		

Note: The blue circles represent observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed red lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same.

Source: Applicant's PopPK/PD report. Figures 9.4 to 9.9

4.3.2.1.2. Reviewer's Comments for Applicant's PopPK Analysis

Comment 1

The following comments (Comment 1) were sent to Applicant on 3/7/2022:

The VPC plots (Figure 2 and Figure 3) show that the developed PopPK models underpredict insulin lispro concentrations in children during the initial 1 hour after SC administration for both Lyumjev and Humalog. Since Lyumjev is a rapid-acting human insulin analog, accurately predicting insulin lispro concentrations after dosing is critical to ensure that accurate insulin lispro exposure is used in the IGI model. Therefore, an information request was sent to applicant recommend further improving the PopPK model in children to support extrapolation analysis for LY900014 postmeal or via CSII therapy.

Applicant's IR Response for the Above Comment 1 (received on 3/28/2022):

To further improve the MDI PopPK and PK/PD models for children, the Applicant further optimized the model using only the children's data in Part A of Study ITSA.

As the CSII PopPK model are different from the MDI PopPK models, no further optimization of the CSII PopPK model was conducted for children as the VPC plots showed good agreement between the median of the observed and the 95% CI around the median of the simulated data.

- Further optimization of the PopPK Model for Children with T1D (Study ITSA)

The PK parameters for optimized insulin lispro MDI PopPK model based on reviewer's suggestions were summarized in **Table 6.** Model evaluation based on visual predictive checks plots are shown **in Figure 4.**

Table 6. Pharmacokinetic Parameters for Final Optimized Insulin Lispro MDI PopPK Model Following Subcutaneous Administration of LY900014 and Humalog in Children, Adolescents, and Adults with T1D versus Children with T1D in Study ITSA

		Study ITSA (Part A): Children, Adolescents, and Adults with T1D				Study ITSA (Part A): Children with T1D				
Parameter		**Estimate (%RSE)**		**% Variability(%RSE)**		**Estimate (%RSE)**		**% Variability (%RSE)**	**Bootstrap (N=400) Median**	**95% CI**
Clearance (CL) (L/h)	Θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.6 *fix*[b]	Θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.6 *fix*[b]	28.6 *fix*[a]	28.6 *fix*[c]
Central volume IV (V2_IV) (L)	Θ_2	4.73 *fix*[a]	$\omega_{2,2}$	6.25 *fix*[a]	Θ_2	4.73 *fix*[a]	$\omega_{2,2}$	6.25 *fix*[a]	4.73 *fix*[c]	4.73 *fix*[c]
Central volume SC (V2_SC) (L)	Θ_9	17.4 *fix*[c]	$\omega_{5,5}$	43.0 *fix*[c]	Θ_9	17.4 *fix*[c]	$\omega_{5,5}$	43.0 *fix*[c]	17.4 *fix*[c]	17.4 *fix*[c]
Intercompartmental clearance 1 (Q) (L/h)	Θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.8 *fix*[a]	Θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.8 *fix*[a]	3.89 *fix*[c]	3.89 *fix*[c]
Peripheral volume 1 (V3) (L)	Θ_4	1.49 *fix*[a]	$\omega_{7,7}$	24.6 *fix*[a]	Θ_4	1.49 *fix*[a]	$\omega_{7,7}$	24.6 *fix*[a]	1.49 *fix*[c]	1.49 *fix*[c]
Fraction absorbed via transit compartments (FR_{fo})	Θ_5	0.872 *fix*[b]	$\omega_{9,9}$	0 *fix*	Θ_5	0.872 *fix*[b]	$\omega_{9,9}$	0 *fix*	0.872 *fix*[c]	0.872 *fix*[c]
Mean transit time (MTT) (h)	Θ_6	1.18 *fix*[c]	$\omega_{3,3}$	50 *fix*[c]	Θ_6	0.92 (0.8)	$\omega_{3,3}$	44	0.893	(0.671-1.13)
Duration of zero-order absorption (DUR) (h)	Θ_7	0.239 *fix*[c]	$\omega_{4,4}$	42.2 *fix*[c]	Θ_7	0.239 *fix*[c]	$\omega_{4,4}$	42.2 *fix*[c]	0.239 *fix*[c]	0.239 *fix*[c]
Bioavailability (BIO)	Θ_8	0.542 *fix*[c]	$\omega_{8,8}$	31.4 *fix*[c]	Θ_8	0.542 *fix*[c]	$\omega_{8,8}$	31.4 *fix*[c]	0.542 *fix*[c]	0.542 *fix*[c]
First-order absorption rate constant (K_a) (h^{-1})	Θ_{10}	2.63 *fix*[c]	$\omega_{10,10}$	78.7 *fix*[c]	Θ_{10}	2.63 *fix*[c]	$\omega_{10,10}$	78.7 *fix*[c]	2.63 *fix*[c]	2.63 *fix*[c]
Intercompartmental clearance 2 (Q2) (L/h)	Θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	Θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	1.73 *fix*[c]	1.73 *fix*[c]
Peripheral volume 2 (V4) (L)	Θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	Θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	2.0 *fix*[c]	2.0 *fix*[c]
Differences in Humalog® relative to LY900014										

		Study ITSA (Part A): Children, Adolescents, and Adults with T1D				Study ITSA (Part A): Children with T1D				
Parameter		**Estimate (%RSE)**		**% Variability(%RSE)**		**Estimate (%RSE)**		**% Variability (%RSE)**	**Bootstrap (N=400) Median**	**95% CI**
Fraction absorbed via transit compartments	Θ_{13}	0.14 *fix*[b]		N/A	Θ_{13}	0.14 *fix*[b]		N/A	0.14 *fix*[c]	0.14 *fix*[c]
First-order absorption rate constant (K_a) (h^{-1}) for Humalog	Θ_{14}	-0.774 (7.8)		N/A	Θ_{14}	-0.80 (0)		N/A	-0.798	-0.863--0.702
Differences in T1D relative to healthy subjects										
Bioavailability for T1D	Θ_{15}	-0.39 (57)		N/A	Θ_{15}	-0.36 (1.8)		N/A	-0.364	-0.426--0.304
First-order absorption rate constant for T1D (K_a) (h^{-1})	Θ_{17}	3.58 (0.2)		N/A	Θ_{17}	3.45 (0.2)		45	3.30	1.92-4.73
Central volume SC for T1D (L)	Θ_{19}	0.179 (1.6)		N/A	Θ_{19}	0.304 (0.3)		44	0.337	0.080-0.843
Duration of zero-order absorption T1D (h)	Θ_{21}	3.88 (0)		N/A	Θ_{21}	4.13 (0)		62	3.52	2.08-4.54
Allometric coefficient for bodyweight effect										
Clearance		0.553		N/A	Θ_{23}	0.553*fix*		N/A	N/A	N/A
Central volume		1.06		N/A	Θ_{24}	1.06*fix*		N/A	N/A	N/A
Proportional error (%)	$\delta_{1,1}$	35 (0)		N/A	$\delta_{1,1}$	31 (0)		N/A	31	25-35

Abbreviations: CI = confidence interval; HV = healthy volunteers; IV = intravenous administration route; N =number; %RSE = relative standard error of the estimate as a percentage; PK = pharmacokinetics; N/A = not applicable; SC = subcutaneous administration route; T1D = type 1 diabetes mellitus

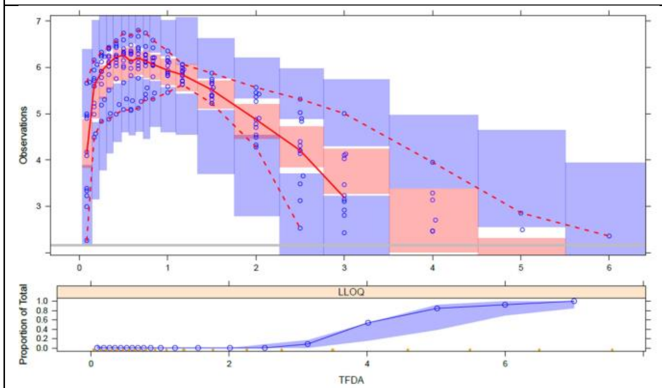
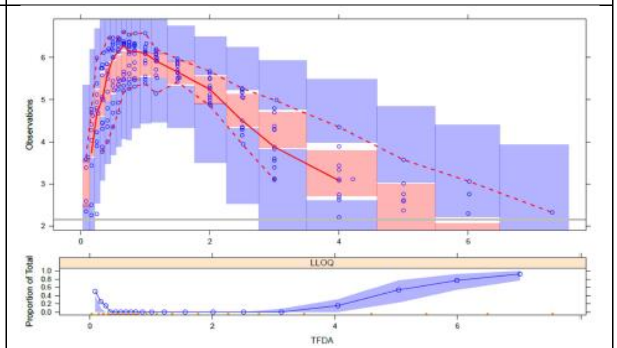
Note: Shaded rows indicated where optimized model has different estimates from the pediatric and adult model.

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.

[c] Parameter values were fixed to the estimates from the Final Full IV+SC model for LY900014 and Humalog.
Source: Applicant's IR response dated 3/28/2022. Table 8.1

Figure 4. Visual predictive checks of the PopPK model predictions of serum insulin lispro concentration following SC administration of a 0.2-U/kg dose of LY900014 and Humalog in children with T1D via MDI.

LY900014	***Humalog***
	

Source: Applicant's IR response dated 3/28/2022. Figure 8.1 and Figure 8.2

The reviewer determined that the revised PopPK is considered acceptable.

4.3.2.1.3. Simulations using the final optimized PopPK model

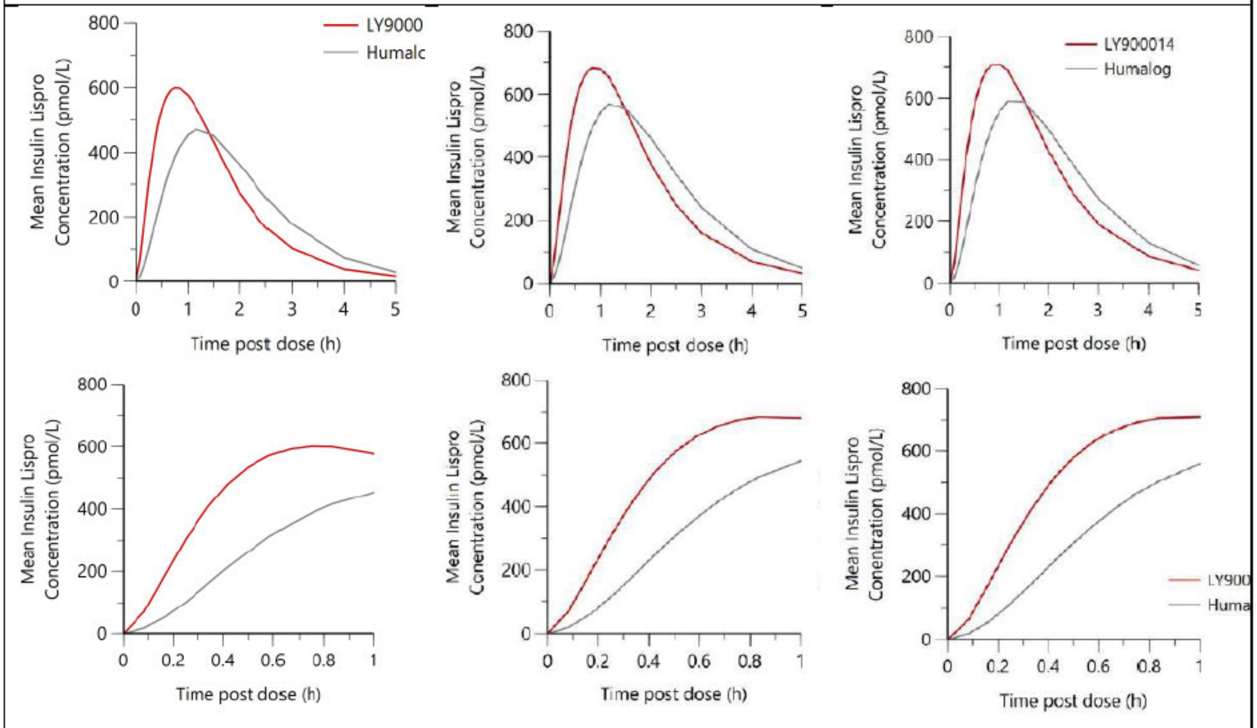
Prediction of Insulin Lispro Concentrations Following LY900014 and Humalog via MDI administration in Children, Adolescents, and Adults with T2DM

PK, efficacy and safety of LY900014 has not been studies in clinical trials in patients with T2DM. In order to understand the PK characteristics of insulin lispro following LY900014 and Humalog in pediatric T2DM patients, simulations were conducted to predict insulin lispro concentrations following LY900014 and Humalog via MDI administration in children, adolescents, and adults with T2DM. The final optimized MDI PopPK model for T1DM patients for children, adolescents, and adults were used for simulation, and population covariates difference between for T1DM and T2DM patients were adjusted.

From the model simulation for T2DM patients, LY900014 showed an accelerated insulin lispro absorption with a reduction in late insulin exposure compared to Humalog across all 3 age groups. An accelerated insulin lispro absorption with LY900014 was quantified by an earlier onset of appearance and early 50% t_{max}, and an increase in the $AUC_{0\text{-}15min}$, $AUC_{0\text{-}30min}$, and $AUC_{0\text{-}1h}$ compared to Humalog based on the central tendency of the model simulations.

Figure 5. Model-predicted mean insulin lispro concentration versus time (top) and for the first hour post dose (bottom) following SC injection via MDI of a 0.2 U/kg dose of either LY900014 or Humalog in children (left), adolescents (middle), and adults (right) with T2DM.

Children	Adolescents	Adults



Abbreviations: h = hour; SC = subcutaneous; T2D = type 2 diabetes mellitus.

Source: Applicant's pediatric/adult MDI Population PK/PD reports. Figure 10.2.

Applicant's IR response on 03/28/2022. Figure 9.2

4.3.2.2. PK/PD Analysis

4.3.2.2.1. Applicant's PK/PD Analysis

Objectives

The objectives of the applicant's PK/PD analyses were to:

- characterize the exposure-response relationship between insulin lispro concentration and postprandial glucose (PPG) lowering following SC administration of either LY900014 or Humalog in pediatric patients with T1DM following MDI or CSII therapy based on available clinical data from ITSA study. The IGI model is used to explain the impact of accelerated absorption for PK profiles of LY900014 as compared to Humalog on postprandial glucose profiles.
- predict the PPG response following SC injection of either LY900014 or Humalog in pediatric patients with T2DM in which T2DM patients were not studies in clinical trials.

- characterize the PK/PD relationship between insulin lispro concentration and postprandial glucose (PPG) lowering following SC infusion of either LY900014 or Humalog administered 20 min after start of a MMTT in pediatric patients with T1DM, in which post-meal scenario was not studied in Study ITSA.

<u>Methods</u>

T1D PK/PD model

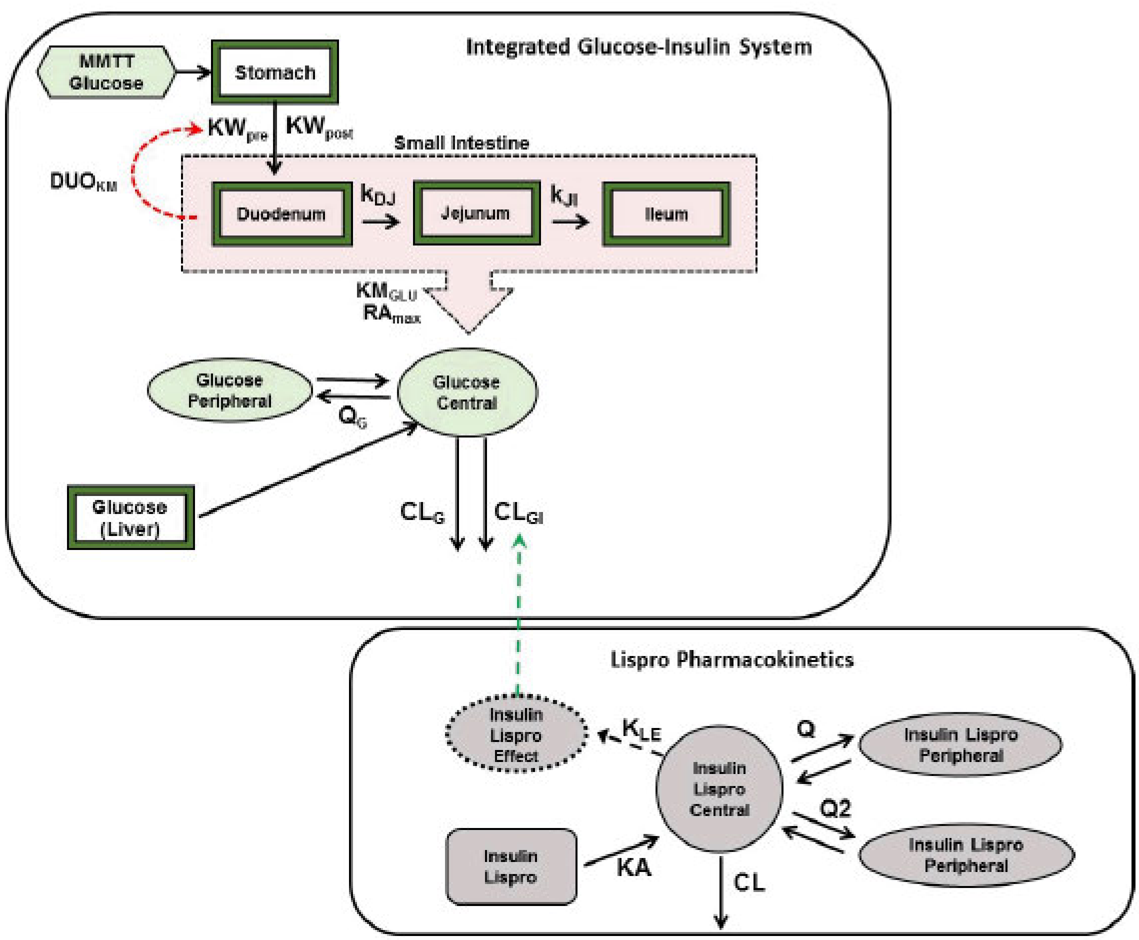
- Final Adult T1DM IGI model

The IGI model (published previously by Silber et al, J Clin Pharmacol. 2010 Mar; 50(3):246-56) is a mechanistic PK/PD model that incorporates the effects of endogenous glucose and insulin as follows:

- the stimulatory effect of insulin on glucose elimination
- the glucose absorbed into the body was calculated from carbohydrate contents in the meals.

In general, the adult IGI model (**Figure 6**) for patients with T1DM for insulin lispro is acceptable (refer to BLA 761109 Insulin lispro OCP review by Dr. Sista and Dr. Li darrts on 05/06/2020).

Figure 6. PK/PD Adult/Pediatric T1DM IGI model



Abbreviations: CL = insulin lispro clearance; CLG = insulin-independent glucose clearance; CLGI = insulin-dependent glucose clearance; DUOKM = amount of glucose in the duodenum giving 50% of maximum inhibition of gastric emptying; IGI = integrated insulin-glucose; KA = insulin lispro first-order absorption rate constant; kDJ = rate constant for glucose movement from the duodenum to jejunum; kJI = rate constant for glucose movement from the jejunum to ileum; kLE = rate constant for insulin lispro effect compartment related to CLGI; KMGLU = amount of glucose giving 50% of maximum absorption; KWpre = gastric emptying rate for premeal dosing; KWpost = gastric emptying rate for meal for postmeal dosing; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics; Q = intercompartmental clearance between insulin lispro central compartment and peripheral compartment 1; Q2 = intercompartmental clearance between insulin lispro central compartment and peripheral compartment 2; QG = intercompartmental clearance between glucose central and glucose peripheral compartments;; RAmax = maximum rate of absorption from the small intestine; T1DM = type 1 diabetes mellitus.
Source: Applicant's Population PK/PD MDI model. Figure 8.2.

- Optimization of the Final Adult T1DM IGI Model for Children, Adolescents, and Adults with T1DM (Study ITSA)

Based on prior experience of modeling insulin lispro in adults with T1DM, the following parameters relating to glucose absorption and insulin effect were estimated based on updated data from Study ITSA:

- KM_{GLU} (amount of glucose giving 50% of maximum absorption)
- DUO_{KM} (amount of glucose in the duodenum giving 50% of maximum inhibition of gastric emptying)
- KW_{pre} (gastric emptying rate for premeal dosing)
- EC_{50} (amount of insulin giving 50% of maximum inhibition of glucose production) and HILL (shape parameter for insulin inhibition of glucose production)
- CL_{GI} (insulin-dependent glucose clearance)

All other parameter values, including interindividual and residual variability, were fixed to the estimates in IGI T1DM adult model.

The fit of the final model to the data in pediatric patients with T1DM was evaluated using simulation-based diagnostics (VPCs).

Simulations

- Prediction of Postprandial Glucose Concentrations Following LY900014 and Humalog When Injected 20 minutes after the Start of a MMTT in Children, Adolescents, and Adults with T1DM

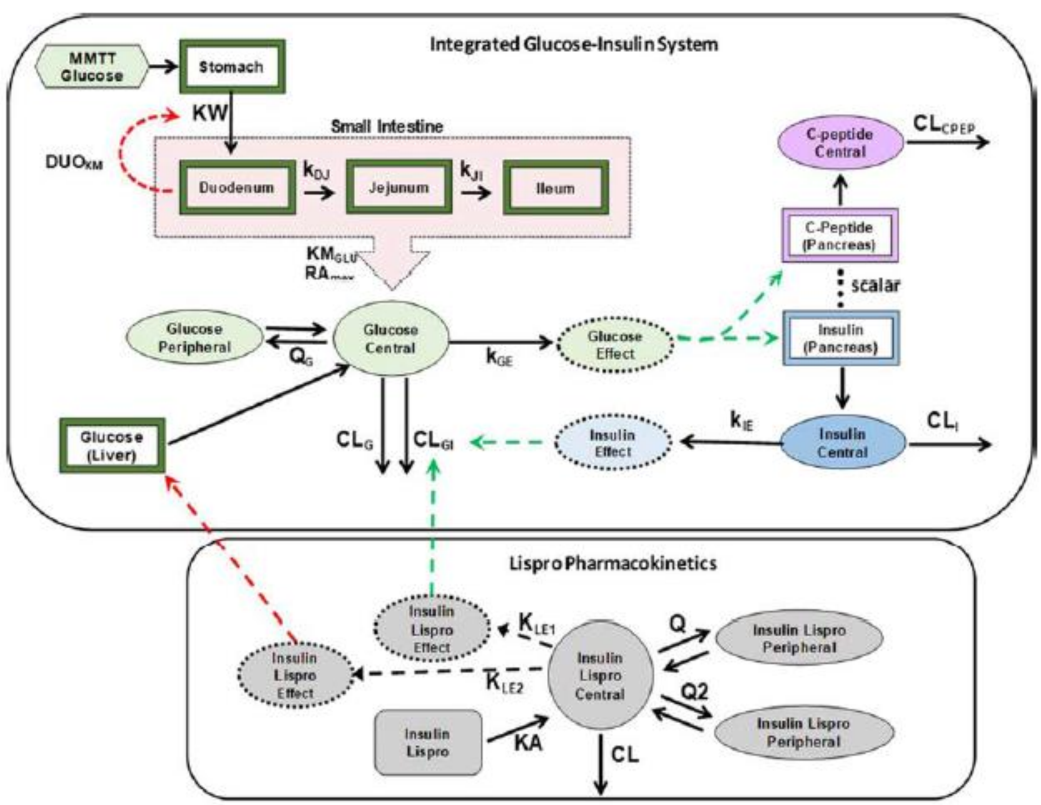
The optimized final PK/PD model was used to simulate glucose time course following MMTT when LY900014 or Humalog was administered 20 minutes after the start of the meal. The simulations used the ITSA study population, MMTT content, and insulin dosing (0.2 U/kg) given 20 minutes after the start of the meal.

- Prediction of Postprandial Glucose Concentrations Following LY900014 and Humalog When Injected Immediately before and 20 minutes after the Start of a MMTT in Children, Adolescents, and Adults with T2DM

The adult T2DM PK/PD model was reviewed previously (refer to BLA 761109 Insulin lispro OCP review by Dr. Sista and Dr. Li darrts on 05/06/2020).

The adult T2DM PK/PD model was adjusted for pediatrics and children based on the changes made between the PK/PD model in adult patients with T1DM and the final optimized PK/PD model for adults, children, and adolescents with T1DM in Study ITSA (pediatric/adult T1DM MDI PK/PD model). After finalizing the pediatric/adult T2DM PK/PD model, glucose time course was simulated following MMTT when either LY900014 or Humalog administered immediately prior or 20 minutes after the start of the meal. The simulations used the ITSA study population (children, adolescents, and adults), MMTT content, and insulin dosing (0.2 U/kg) given immediately prior to the meal or 20 minutes after the start of the meal as the condition.

Figure 7. PK/PD Adult/Pediatric T2DM IGI model.



Abbreviations: CL = insulin lispro clearance; CLCPEP = C-peptide clearance; CLG =insulin-independent glucose clearance; CLGI = insulin-dependent glucose clearance; CLI = endogenous insulin clearance;

DUOKM = amount of glucose in the duodenum giving 50% of maximum inhibition of gastric emptying; IGI = integrated insulinglucose; KA = insulin lispro absorption rate; kDJ = rate constant for glucose movement from the duodenum to jejunum; kGE = rate constant for glucose effect compartment; kIE = rate constant for endogenous insulin effect compartment; kJI = rate constant for glucose movement from the jejunum to ileum; KLE1 = rate constant for insulin lispro effect compartment related to CLGI; KLE2 = rate constant for insulin lispro effect compartment related to hepatic glucose production; KMGLU = amount of glucose giving 50% of maximum absorption; KW = gastric emptying rate; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics; Q = clearance between insulin lispro central compartment and peripheral compartment 1; Q2 = clearance between insulin lispro central compartment and peripheral compartment 2; QG = intercompartmental clearance between glucose central and glucose peripheral compartments; RAmax = maximum rate of absorption from the small intestine; T2DM = type 2 diabetes mellitus.
Source: Applicant's Population PK/PD MDI model. Figure 8.3.

Results

- Final Optimized T1DM PK/PD Model for adults, adolescents and children.

Table 7. Parameter Estimates of the Optimized Integrated Glucose-Insulin Model for T1DM patients (Study ITSA)

Model		Adult T1DM IGI Base Model		Study ITSA (Part A): Children, Adolescents, and Adults with T1DM			
Parameter		Estimate (%RSE)	IIV (%CV)	Estimate (%RSE)	IIV (%CV)	Bootstrap Median (95% CI)	Bootstrap IIV (%CV)
Gastric emptying							
Emptying rate predose (/min) (KW_{pre})	θ_{19}	0.0458 *fix*[g]	135 *fix*[g]	0.0207 (7.6)	135 *fix*[g]	0.0200 (0.0086, 0.0306)	135 *fix*[g]
Emptying rate postdose (/min) (KW_{post})	θ_{20}	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]
Amount of glucose in the duodenum giving 50% of maximum inhibition of gastric emptying (cg) (DUO_{KM})	θ_2	474 (13.3)	73.3 (10.2)	188 (8.3)	42	173 (147, 221)	47 (22, 66)
Shape parameter for glucose inhibition (GAMMA)	θ_3	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]
Delay in emptying for the meal (min)	θ_8	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]
Glucose absorption							
Maximum rate of absorption from the duodenum (cg/h)	θ_{13}	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]
Maximum rate of absorption from the jejunum (cg/h)	θ_{14}	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]
Maximum rate of absorption from the ileum (cg/h)	θ_{15}	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]
Amount of glucose giving 50% of maximum absorption (cg) (KM_{GLU})	θ_{12}	2290 (8.7)	7.1 *fix*[f]	127 (6.2)	7.1 *fix*[f]	112 (89.1, 154)	7.1 *fix*[f]
First-pass effect on glucose	θ_1	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]
Glucose disposition							
Insulin-independent glucose clearance (L/h)	θ_4	1.89 *fix*[c]	59.3 *fix*[d]	1.89 *fix*[c]	59.3 *fix*[d]	1.89 *fix*[c]	59.3 *fix*[d]
Maximum insulin-dependent glucose clearance (L/h) Adult		21.8 *fix*[e]	54.0 *fix*[e]	11.4 (20)	75	11.7 (7.53, 15.0)	65 (25-104)
Maximum insulin-dependent glucose clearance (L/h) Adolescents		NA	NA	7.42 (22)	75	6.86 (3.84, 10.3)	65 (25-104)
Maximum insulin-dependent glucose clearance (L/h) Children		NA	NA	8.32 (24)	75	6.72 (2.70, 13.5)	65 (25-104)
Central volume of distribution (L)	θ_6	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]
Peripheral volume of distribution (L)	θ_7	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]
Intercompartmental clearance (L/h)	θ_9	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]

Rate constant for glucose effect compartment (/h) (K_{LE})	θ_{10}	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]
Formation of endogenous glucose during the meal period (mg)	θ_{16}	4.79 (14)	7.1 *fix*[f]	1.34 (27)	7.1 *fix*[f]	1.27 (1.11, 1.45)	7.1 *fix*[f]
Concentration of insulin lispro giving 50% of maximum insulin-dependent glucose clearance (pmol/mL)	θ_{17}	338 (9.4)	7.1 *fix*[f]	244 (2.8)	7.1 *fix*[f]	233 (194, 290)	7.1 *fix*[f]
Shape parameter for insulin lispro	θ_{18}	1.86 (10.4)	7.1 *fix*[f]	21.3 (20)	7.1 *fix*[f]	22.5 (5.68, 40.9)	7.1 *fix*[f]
Residual variability (%)	θ_{11}	22 (1.4)		42 (1.8)		42 (39, 45)	

Abbreviations: CI = confidence interval; CSII = continuous subcutaneous insulin infusion; CV = coefficient of variation; IGI = integrated insulin-glucose; IIV = interindividual variability; %RSE = relative standard error of the estimate as a percentage; SAEM = stochastic approximation expectation maximization; 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.

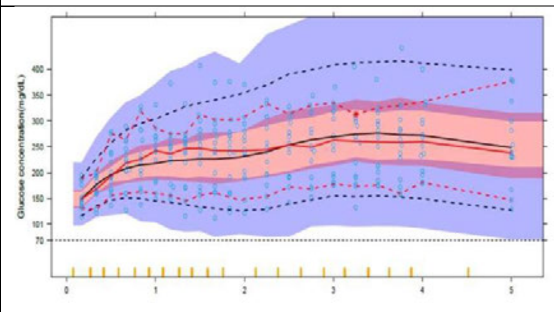
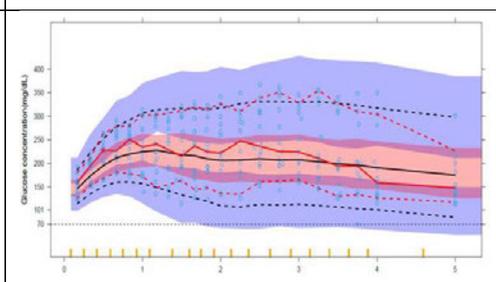
e. Fixed to value from CSII model (Lilly data on file).

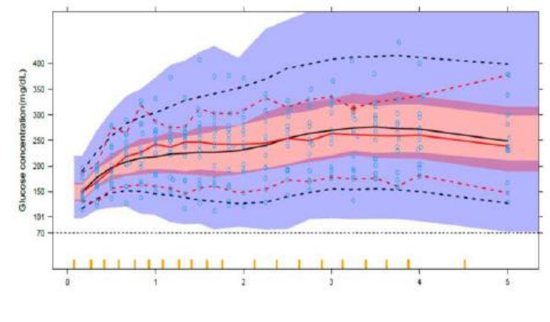
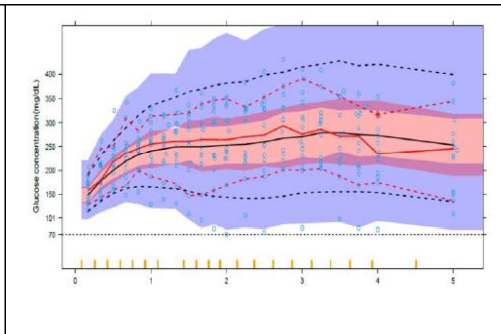
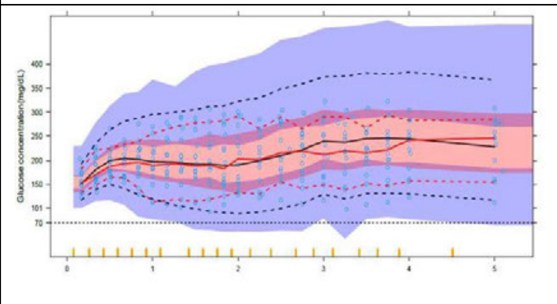
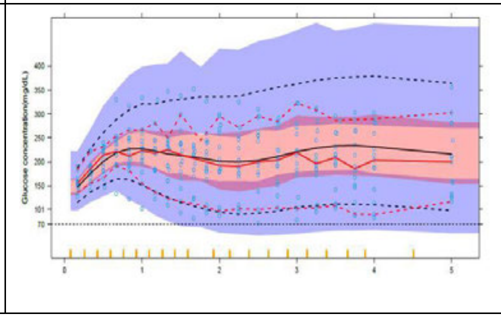
f. Fixed to facilitate efficient operation of the SAEM algorithm.

g. Fixed to value from sensitivity analysis.

Source: Population PK/PD MID modeling report.

Figure 8. Visual predictive check of the model predictions of glucose concentration during the breakfast MMTT following administration of LY900014 or Humalog immediately prior to the start of the meal in adults with T1DM using the final optimized PK/PD model (Study ITSA).

	LY900014	Humalog
Children		

Adolescent		
Adults		
Abbreviations: MMTT = mixed meal tolerance test; T1DM = type 1 diabetes mellitus. Note: The blue circles represent observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed red lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same. 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: Population PK/PD MID modeling report. Figures 9.12 to 9.17.		

4.3.2.2.2. Reviewer's Comments for Applicant's PK/PD Analysis

Comment 2

The following Comments (Comment 2) were sent to Applicant on 3/7/2022:

It is observed in the VPC plots (**Figure 8**) for the final type 1 PK/PD IGI model that the developed model underpredicted the mean glucose concentrations following intervention in children. Validated PopPK and PK/PD models in all age groups are fundamental for supporting extrapolation analysis for LY900014 postmeal and/or via CSII therapy. Therefore, we recommend the Applicant further improve the PK/PD models in children to support extrapolation analysis for LY900014 postmeal or via CSII therapy.

Applicant's IR Response for Comment 2 (received on 3/28/2022):

To further improve the MDI PK/PD models for children, the models were optimized using only the children's data in Part A of Study ITSA.

As the CSII popPK and PK/PD models are different from the MDI popPK and PK/PD models, no further optimization of the CSII PK and PK/PD models was conducted for children as the VPC plots showed good agreement between the median of the observed and the 95% CI around the median of the simulated data.

The optimized children Type 1 PK/PD model is summarized as below.

Table 8. Parameter Estimates of the Optimized Integrated Glucose-Insulin Model for T1DM Children (ITSA)

Model		Study ITSA (Part A): Children, Adolescents, and Adults with T1D				Study ITSA (Part A): Children with T1D			
Parameter		**Estimate (%RSE)**	**IIV (%CV)**	**Bootstrap Median (95% CI)**	**Bootstrap IIV (95% CI)**	**Estimate (%RSE)**	**IIV (%CV)**	**Bootstrap Median (95% CI)**	**Bootstrap IIV (95% CI)**
Gastric emptying									
Emptying rate predose (/min) (KW_{pre})	θ_{19}	0.0207 (7.6)	135 *fix*[g]	0.0200 (0.0086, 0.0306)	135 *fix*[g]	0.0154 (71.4)	135 *fix*[g]	0.0150 (0.0118, 0.0403)	135 *fix*[g]
Emptying rate postdose (/min) (KW_{post})	θ_{20}	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]
Amount of glucose in the duodenum giving 50% of maximum inhibition of gastric emptying (cg) (DUO_{KM})	θ_{2}	188 (8.3)	42	173 (147, 221)	47 (22, 66)	115 (15.8)	42*fix*	86.8 (48.3, 134)	42*fix*
Shape parameter for glucose inhibition (GAMMA)	θ_{3}	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]
Delay in emptying for the meal (min)	θ_{8}	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]
Glucose absorption									
Maximum rate of absorption from the duodenum (cg/h)	θ_{13}	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]
Maximum rate of absorption from the jejunum (cg/h)	θ_{14}	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]
Maximum rate of absorption from the ileum (cg/h)	θ_{15}	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]
Amount of glucose giving 50% of maximum absorption (cg) (KM_{GLU})	θ_{12}	127 (6.2)	7.1 *fix*[f]	112 (89.1, 154)	7.1 *fix*[f]	55.4 (16.9)	7.1 *fix*[f]	37.5 (23.1, 47.3)	7.1 *fix*[f]
First-pass effect on glucose	θ_{1}	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]
Glucose disposition									
Insulin-independent glucose clearance (L/h)	θ_{4}	1.89 *fix*[e]	59.3 *fix*[d]	1.89 *fix*[e]	59.3 *fix*[d]	1.89 *fix*[e]	59.3 *fix*[d]	1.89 *fix*[e]	59.3 *fix*[d]
Maximum insulin-dependent glucose clearance (L/h) Adult		11.4 (20)	75	11.7 (7.53, 15.0)	65 (25, 104)	NA	NA	NA	NA
Maximum insulin-dependent glucose clearance (L/h) Adolescents		7.42 (22)	75	6.86 (3.84, 10.3)	65 (25,104)	NA	NA	NA	NA
Maximum insulin-dependent glucose clearance (L/h) Children		8.32 (24)	75	6.72 (2.70, 13.5)	65 (25-104)	5.13 (49.3)	163	5.50 (1.84, 15.4)	173 (74.6-307)
Central volume of distribution (L)	θ_{6}	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]
Peripheral volume of distribution (L)	θ_{7}	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]
Intercompartmental clearance (L/h)	θ_{9}	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]
Rate constant for glucose effect compartment (/h) (K_{LE})	θ_{10}	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]
Formation of endogenous glucose during the meal period (mg) ($Base_{GLU}$)	θ_{16}	1.34 (27)	7.1 *fix*[f]	1.27 (1.11, 1.45)	7.1 *fix*[f]	0.558 (12.2)	7.1 *fix*[f]	0.646 (0.441, 0.838)	7.1 *fix*[f]
Concentration of insulin lispro giving 50% of maximum insulin-dependent glucose clearance (pmol/L)	θ_{17}	244 (2.8)	7.1 *fix*[f]	233 (194, 290)	7.1 *fix*[f]	244 *fix*	7.1 *fix*[f]	244 *fix*	7.1 *fix*[f]
Shape parameter for insulin lispro	θ_{18}	21.3 (20)	7.1 *fix*[f]	22.5 (5.68, 40.9)	7.1 *fix*[f]	21.3 *fix*	7.1 *fix*[f]	21.3 *fix*	7.1 *fix*[f]
Residual variability (%)	θ_{11}	42 (1.8)		42 (39, 45)		44 (3.6)		45 (40, 49)	

Abbreviations: CI = confidence interval; CSII = continuous subcutaneous insulin infusion; CV = coefficient of variation; IGI = integrated insulin-glucose; IIV =interindividual variability; %RSE = relative standard error of the estimate as a percentage; SAEM = stochastic approximation expectation maximization; T1D = type 1 diabetes mellitus.

Note: Shaded rows indicated where optimized model has different estimates from the pediatric/adult model.

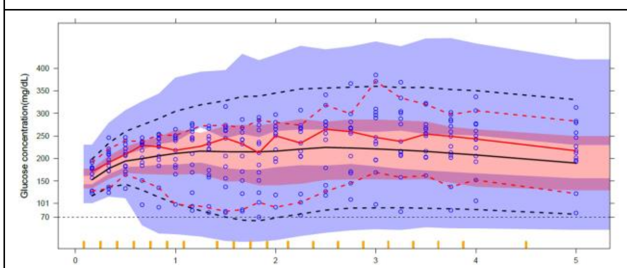
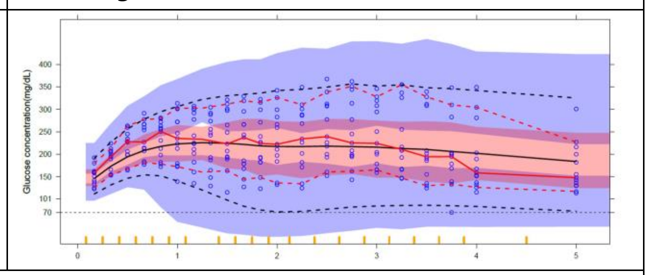
a. Fixed to value from Alskär et al. 2016.
b. Fixed to value from Hovorka et al. 2004.
c. Fixed to value from Silber et al. 2010.
d. Fixed to value from Schneck et al. 2013.
e. Fixed to value from CSII model (Lilly data on file).
f. Fixed to facilitate efficient operation of the SAEM algorithm.
g. Fixed to value from sensitivity analysis.

Applicant's IR response on 03/28/2022.

Model Evaluation

VPCs were performed on the optimized children Type 1 PK/PD model to confirm that the models were able to correctly predict all data. The observed data were plotted on the normal scale (mg/dL) and plotted against the time (hour) relative to the start of the meal.

Figure 9. Visual predictive check of the model predictions of glucose concentration during the breakfast MMTT following administration of Humalog immediately prior to the start of the meal in children with T1D for the base pediatric model (left) and optimized children model (right) (Study ITSA).

LY900014	***Humalog***
	

Abbreviations: MMTT = mixed meal tolerance test; T1D = type 1 diabetes mellitus.
Note: The blue circles represent observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed red lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same. The solid black line represents the median of the prediction, and the black dashed lines represent the lower and upper bounds of the 90% prediction interval.

Applicant's IR response on 03/28/2022. Figure 8.5

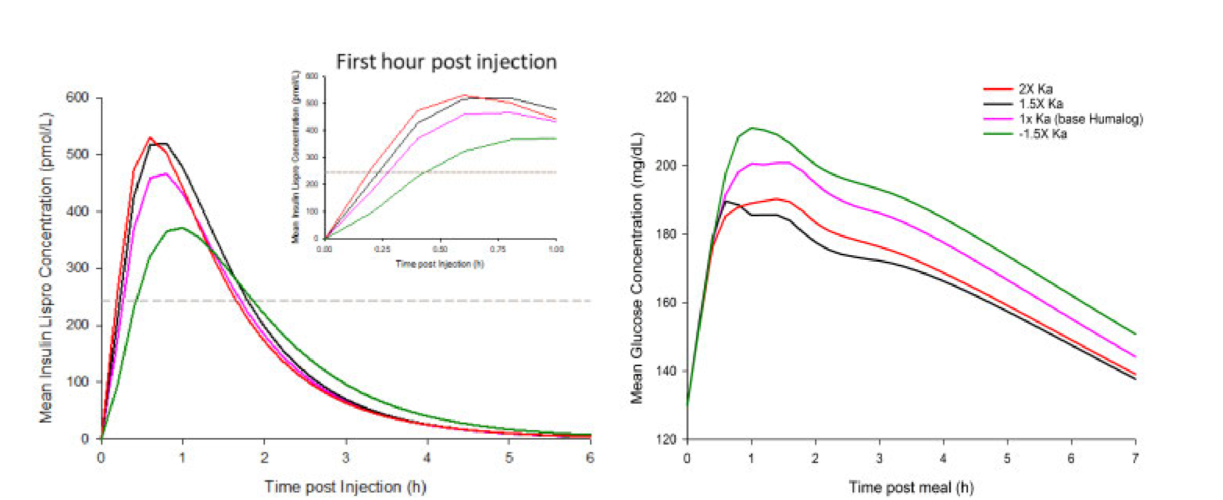
The result of VPCs showed that the optimized final children population PK/PD model for T1DM improved the fit by bringing the median model predictions closer to the median of the observed glucose concentrations. Based on the model predicted 95% CI of 5th and 95th percentiles of the observed data, the model also captured the IIV observed in children in Study ITSA. Overall, the fit of the glucose profiles was improved with the optimized children PK/PD model compared with the pediatric and /adult PK/PD model. The reviewer determined that this optimized final children population PK/PD model for T1DM patients is acceptable for predicting treatment effect of plasma glucose profiles and projection of hypoglycemia rate post LY900014 and Humalog dose.

Comment 3

The following Comments (Comment 3) were sent to Applicant on 3/7/2022:

Since the original PopPK model slightly overestimate the early insulin lispro exposures (within 1-hour postdose) following dose, it is important to better understand impact of different early insulin lispro exposures on the prediction of the PPG response in children with T1DM. Therefore, we recommend conducting a sensitivity analysis assessing the impact of different early insulin lispro exposures (within 1-hour postdose) on the prediction of glucose in patients with T1DM in children.

Figure 10. Model-simulated insulin lispro profiles versus time (left) and glucose concentration versus time (right) during a breakfast MMTT following SC injection of a 7U dose when insulin was given immediately prior the start of the meal in children with T1D with the optimized PK and PK/PD children models with different insulin absorption rate constants (Ka).



Abbreviations: h = hour; Ka = absorption rate constant; MMTT = mixed meal tolerance test; PK = pharmacokinetic; PK/PD = pharmacokinetic/pharmacodynamic; SC = subcutaneous; T1D = type 1 diabetes mellitus.

Source: Applicant's IR Response for Comment 3 (received on 3/28/2022) .

Additional sensitivity analyses using the optimized children PopPK and PK/PD models were conducted to assess the impact of different early insulin lispro exposures on the prediction of glucose in children with T1DM. Population-level simulations were conducted where the first-order Ka was adjusted within the PK model while keeping all of the other PK and PD parameters fixed and maintaining a 7 U dose and a 30 kg body weight, reflective of the children population from Study ITSA. The PPG response following a MMTT containing 60 grams of carbohydrates was then simulated for the various PK profiles using the children PK/PD IGI model.

The simulation results are shown in **Figure 10**. Reflective of the steep E-R relationship, the rate of the insulin absorption impacts the glucose lowering. This is illustrated within the plots by relating the timing of insulin lispro concentrations to the EC50 estimates from the PK/PD model. Once the insulin lispro concentration reaches the EC50 concentration (gray line), glucose lowering is observed. For example, the insulin absorption is the fastest with the 2x Ka (red line) and achieves the EC50 first of these PK profiles. Correspondingly, the glucose plot shows that it has the earliest glucose lowering response. Likewise, the slowest insulin absorption (-1.5x Ka), shown with the green line, achieves the EC50 later, and also the highest PPG. Although there is a slight difference in Cmax is observed between the 2x Ka (red line) and 1.5x Ka (black line), the PPG responses are very similar. This suggests that small differences in the Cmax may not be as impactful on the PPG response. Overall, this analysis suggested that slight overestimation in early insulin lispro exposures (within 1-hour postdose) may have a minimal impact on the prediction of the PPG response in children with T1DM.

4.3.2.2.3. Simulations using the final optimized PK/PD model

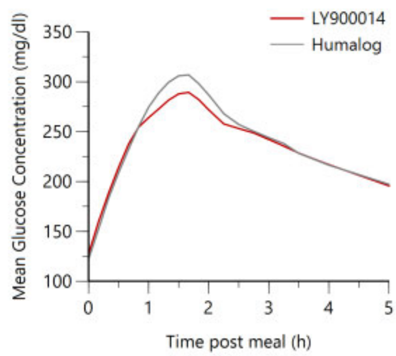
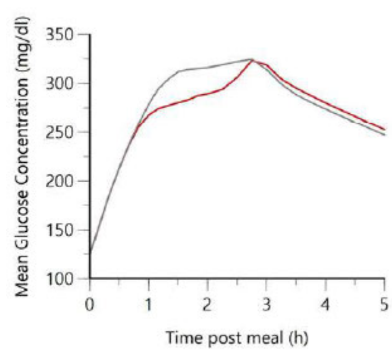
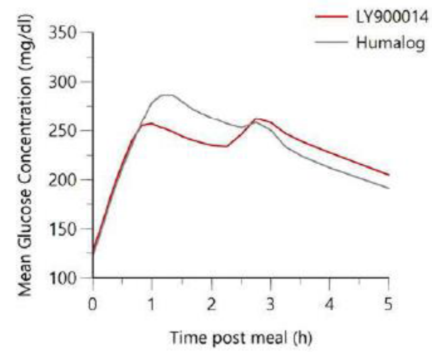
4.3.2.2.3.1. Population Prediction of Postprandial Glucose Concentrations Following Injection of LY900014 and Humalog 20 minutes after the Start of a MMTT in Children, Adolescents, and Adults with T1DM

The optimized final PK/PD model for T1DM was used to simulate glucose time course following MMTT when either LY900014 or Humalog was administered 20 minutes after the start of the meal; this was not evaluated in Study ITSA. The simulations used the ITSA study population, MMTT, and insulin dosing (0.2 U/kg) but given 20 minutes after the start of the meal.

The model predicted that the glucose excursion would be higher for both LY900014 and Humalog when they are given 20 minutes after the start of the meal compared to when the insulin is dosed immediately prior to the start of the meal. Importantly, when both insulins (LY900014 and Humalog) are given 20 minutes after the start of the meal, LY900014 has a greater glucose lowering than Humalog.

These observations align with the PPG response observed in clinical pharmacology study conducted in adults with T2DM (ITRW) where postmeal dosing was assessed for both LY900014 and Humalog and is reflective of the absorption of carbohydrates prior to the onset of insulin action.

Figure 11. Model-predicted mean glucose concentration following SC injection of a 0.2 U/kg dose of either LY900014 or Humalog 20 minutes post the start of the meal in children (left), adolescents (middle), and adults (right) with T1DM.

Children	Adolescents	Adults
		

Abbreviations: h = hour; MMTT = mixed meal tolerance test; SC = subcutaneous; T2D = type 2 diabetes mellitus.

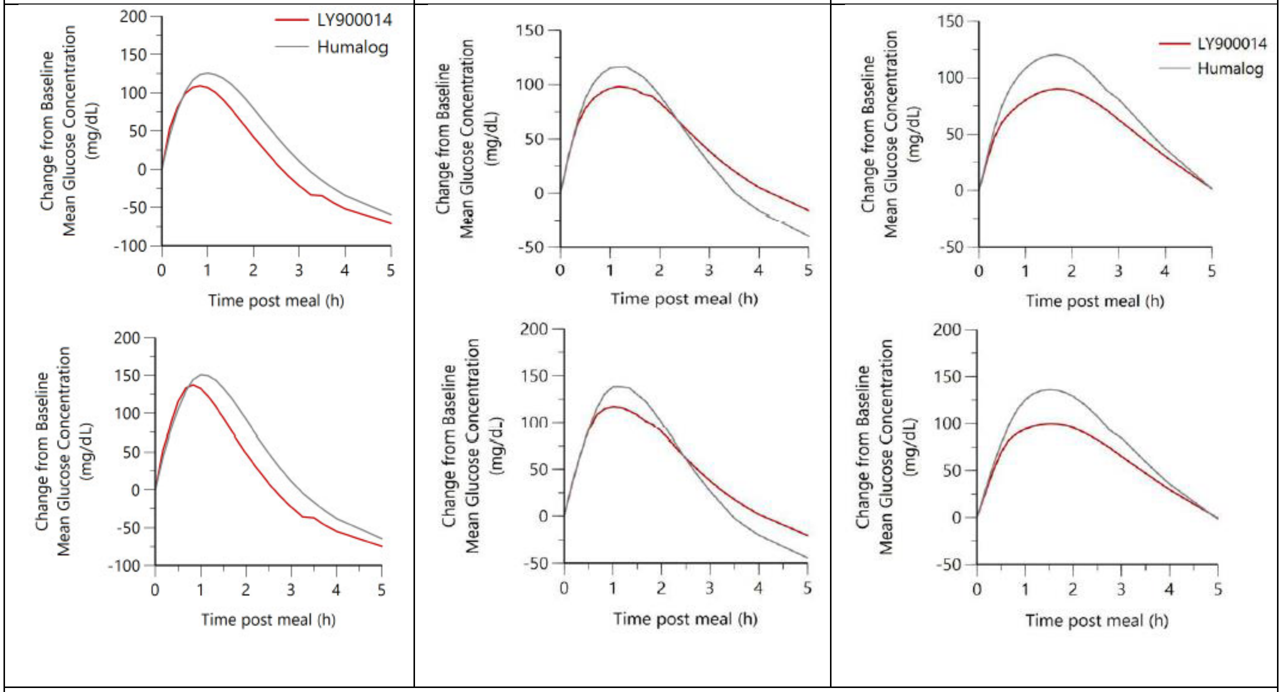
Sources:
Applicant's MDI PopPK/PD report. Figure 10.1
Applicant's IR Response. Figure 9.1 (received on 3/28/2022).

4.3.2.2.3.2. Prediction of Postprandial Glucose Concentrations Following LY900014 and Humalog in Children, Adolescents, and Adults with T2DM via MDI therapy

Similar to the PK predictions in children with T2DM, the adult T2DM PK/PD model was adjusted based on the changes made between the PK/PD model in adult patients with T1D and the optimized PK/PD model for children with T1DM. Model-based simulations showed that when both insulins (LY900014 and Humalog) were given prior to the start of meal or 20 minutes after the start of the meal, LY900014 had a greater glucose lowering effect than Humalog in children with T2DM. Additionally, the model predicted that the glucose excursion would be higher for both LY900014 and Humalog when given 20 minutes after the start of the meal compared to when LY900014 and Humalog are dosed immediately prior to the start of the meal. These observations align with the PPG response observed in clinical pharmacology studies conducted in adults with T2DM (Study -ITRW and Study I8B-FW-ITRH) where postmeal dosing was assessed for both LY900014 and Humalog and is reflective of the absorption of carbohydrates prior to the onset of insulin action.

Figure 12. Model-simulated change from baseline glucose concentration versus time from breakfast MMTT following SC injection of a 0.2-U/kg dose of either LY900014 or Humalog when insulins are given immediately prior (top) and 20 minutes after (bottom) the start of the meal in children (left), adolescents (middle), and adults (right) with T2DM.

Children	Adolescents	Adults



Abbreviations: h = hour; SC = subcutaneous; T2D = type 2 diabetes mellitus.

Sources: Applicant's MDI PopPK/PD report. Figure 10.2
Applicant's IR Response. Figure 9.3 (received on 3/28/2022).

4.3.2.2.3.3. Exposure - Response Analysis for Safety

Since Study ITSA only enrolled subjects down to 8 years of age, the Agency would like to further investigate the hypoglycemia risks for younger kids down to 2 years of age using a simulation approach by PK/PD modeling.

Per the Agency's request (7/21/2022), the Applicant used the final modified IGI models developed for pediatric patients with T1DM and T2DM to perform simulations of the PPG response for children down to 2 years of age. The incidence of hypoglycemia was tabulated with BG ≤70 and BG ≤54 mg/dL at ≤0.5, ≤1, ≤2, ≤4, >1 to ≤2, >2 to ≤3, and >3 to ≤4, and >4 to ≤5 hours.

In addition, since the meal composition for younger kids is different than those of older kids, adolescents, and adults. The Applicant performed sensitivity analysis to evaluate the impact of different levels of carbohydrate intake on the prediction of incidences of hypoglycemia in pediatric patients with T1DM and T2DM.

4.3.2.2.3.3.1. Applicant's Analysis and Response

Simulation Approach to Assess Hypoglycemia Risk for Children Down to 2 years of Age

Method

Simulations were performed using virtual patients reflective of the ITSB Phase 3 children population (body weight, insulin dose, premeal glucose) with an age range of 4 to 11 years at fixed dose level of 10 U. A dataset of 2000 virtual patients was created by randomly selecting the baseline body weight, baseline BG concentration, and individualized insulin lispro dose (LY900014 or Humalog) from the Study ITSB children distribution. To preserve the possible correlation between baseline body weight, baseline BG concentration, and individualized insulin lispro dose (LY900014 or Humalog), all 3 values were randomly selected together as a set of conditions representative of the study population.

Simulated conditions:
1) The PPG response following the MMTT containing 50 g of carbohydrate, representative of 1 can of Ensure® Plus, was simulated.

2) The PPG response following a MMTT containing lower amounts of carbohydrate of 35 g of carbohydrates

3) The PPG response following a MMTT containing lower amounts of carbohydrate of 15 g of carbohydrates

To enable the comparison of LY900014 and Humalog, the conditions for the simulations were similar. The incidence of hypoglycemia, defined by BG ≤70 or BG ≤54 mg/dL at ≤0.5, ≤1, ≤2, ≤4, >1 to ≤2, >2 to ≤3, >3 to ≤4, and >4 to ≤5 hours following administration of LY900014 or Humalog in patients given different amounts of carbohydrates in the MMTT, was calculated and the simulation was repeated 1000 times with a different set of 300 sampled virtual patients each time to reflect the number of patients within each treatment arm of the Phase 3 Study ITSB. To mirror the clinical study where postprandial hypoglycemia events were treated, in each virtual patient only the first occurrence of BG ≤70 or BG ≤54 mg/dL was counted in the summary of the simulations.

Results

T1DM

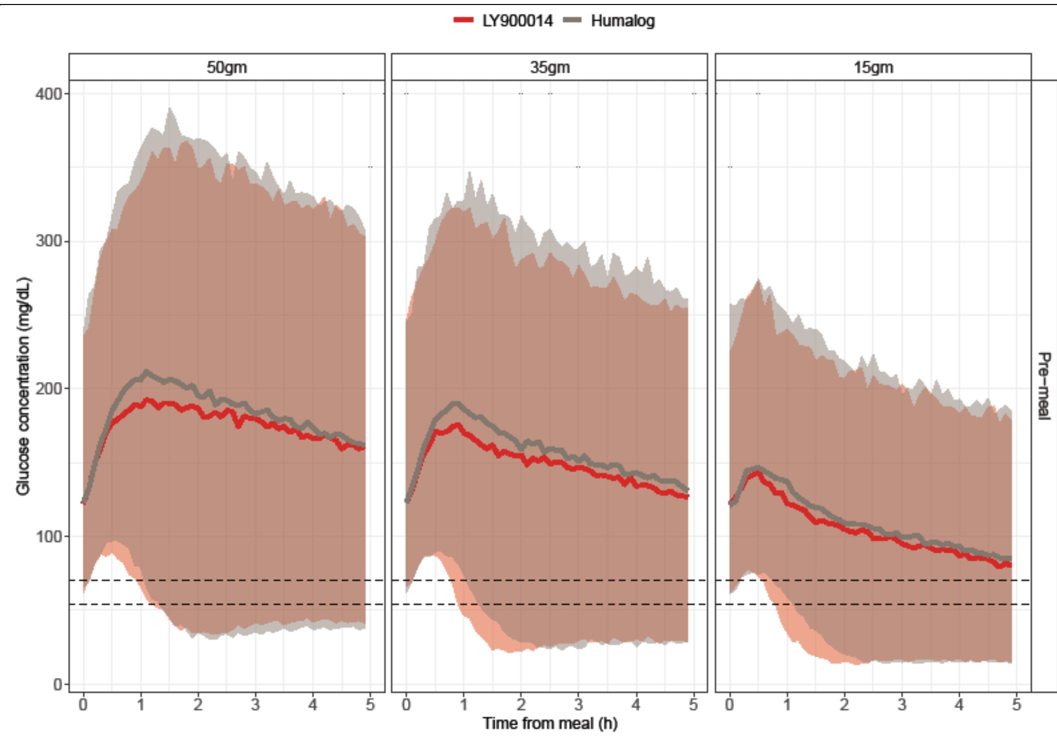
The model-predicted PPG over time profile associated with the MMTT containing 50, 35, or 15 g of carbohydrates with LY900014 or Humalog administered prior to the start of the meal is shown in ***Figure*** 13. Model-predicted glucose time ***course in children with T1DM following*** **an MMTT containing 50 g (left column), 35 g (middle column), or 15 g (right column) of carbohydrate and LY900014 or Humalog given immediately before the start of the meal.**. The simulations incorporated the same insulin dose amounts and showed that the median and range of PPG decreased as the carbohydrate amount in MMTT decreased from 50 to 15 g for both LY900014 and Humalog. The LY900014 treatment consistently showed a lower glucose excursion compared to Humalog and the between-treatment differences were generally similar across all simulated carbohydrate amounts.

Summaries of the number of simulated BG ≤70 or BG ≤54 mg/dL at ≤0.5, ≤1, ≤2, ≤4, >1 to ≤2, >2 to ≤3, >3 to ≤4, and >4 to ≤5 hours following administration of MMTT containing 50, 35, or 15 g of carbohydrates in patients with T1DM given LY900014 or Humalog prior to the start of MMTT are shown in ***Figure 14***, ***Table 9***, and ***Table 10***.

A higher incidence of hypoglycemia was demonstrated in the simulations as the carbohydrate amounts were reduced for the same insulin dose amount, as expected. The median number of simulated BG or BG ≤54 mg/dL over the duration of the MMTT was predominantly higher with LY900014 compared to Humalog; however, the range of simulated number of events for LY900014 and Humalog overlaps for each timing and carbohydrate amount. The relative risk (RR) and relative difference (RD) of LY900014 to Humalog were generally consistent across carbohydrate amounts.

Simulations for Patients with Type 1 Diabetes Mellitus

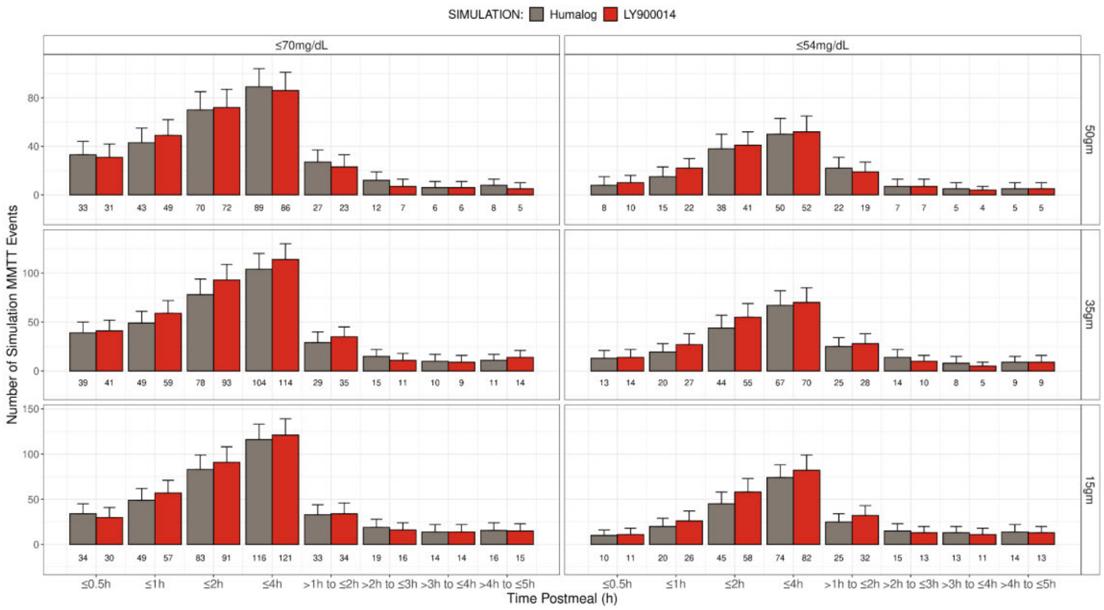
Figure 13. Model-predicted glucose time course in children with T1DM following an MMTT containing 50 g (left column), 35 g (middle column), or 15 g (right column) of carbohydrate and LY900014 or Humalog given immediately before the start of the meal.



Abbreviations: IGI = integrated glucose-insulin; MMTT = mixed meal tolerance test; PI = prediction interval; T1DM = type 1 diabetes mellitus. Note: The solid lines represent the median of the simulation based on the T1DM IGI model and the shaded area denotes the 90% PI.

Source: Applicant's IR response on 7/15/2022. Figure 5.1

Figure 14. Model-predicted glucose ≤70 mg/dL (left column) or ≤54 mg/dL (right column) in children with T1DM following an MMTT containing 50 g (top row), 35 g (middle row), or 15 g (bottom row) of carbohydrates and LY900014 or Humalog given immediately before the meal.



Abbreviations: 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 IR response on 7/15/2022. Figure 5.2

Table 9. Comparison of Model-Predicted Glucose ≤70 mg/dL in Children with T1DM Given Either LY900014 or Humalog Prior to the Start of MMTT

Simulations of		Number of glucose ≤70 mg/dL							
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤3 h	>3 to ≤4 h	>4 to ≤5 h
50 g[a] MMTT	LY900014	31 (22 – 42)	49 (37 – 62)	72 (58 – 87)	86 (71 – 101)	23 (14 – 33)	7 (3 – 13)	6 (2 – 11)	5 (1 – 10)
	Humalog	33 (23 – 44)	43 (31–- 55)	70 (57 – 85)	89 (75 – 104)	27 (18 – 37)	12 (6 - 19)	6 (2 - 11)	8 (3 - 13)
	RR	0.94	1.14	1.03	0.97	0.85	0.58	1.00	0.62
	RD	-2	6	2	-3	-4	-5	0	-3
35 g[a] MMTT	LY900014	41 (29 – 52)	59 (46 – 72)	93 (78– 109)	114 (98 – 130)	35 (24 - 45)	11 (5 – 18)	9 (4 – 16)	14 (8 – 21)
	Humalog	39 (29 – 50)	49 (37 – 61)	78 (65 – 94)	104 (88 – 120)	29 (19 – 40)	15 (8 – 22)	10 (5 - 17)	11 (5 - 17)
	RR	1.05	1.20	1.19	1.10	1.21	0.73	0.90	1.27
	RD	2	10	15	10	6	-4	-1	3
15 g[a] MMTT	LY900014	30 (19 – 41)	57 (44– 71)	91 (76 – 108)	121 (106 – 139)	34 (24 – 46)	16 (9 – 24)	14 (7 – 22)	15 (8 – 23)
	Humalog	34 (24 – 45)	49 (37 – 62)	83 (68 – 99)	116 (101 – 133)	33 (23 – 44)	19 (12 – 28)	14 (8 - 22)	16 (9 - 24)
	RR	0.88	1.16	1.10	1.04	1.03	0.84	1.00	0.94
	RD	-4	8	8	5	1	-3	0	-1

Abbreviations: 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 IR response on 7/15/2022. Table 5.1

Table 10. Comparison of Model-Predicted Glucose ≤54 mg/dL in Children with T1DM Given Either LY900014 or Humalog Prior to the Start of MMTT

Simulations of		Number of glucose ≤54 mg/dL							
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤3 h	>3 to ≤4 h	>4 to ≤5 h
50 g[a] MMTT	LY900014	10 (5 – 16)	22 (14 – 30)	41 (30 – 52)	52 (39 – 65)	19 (11 – 27)	7 (2 – 13)	4 (1 – 7)	5 (1 – 10)
	Humalog	8 (3 – 15)	15 (8 – 23)	38 (28 – 50)	50 (38 – 63)	22 (14 – 31)	7 (3 - 13)	5 (1 – 10)	5 (1 – 10)
	RR	1.25	1.47	1.08	1.04	0.86	1.00	0.80	1.00
	RD	2	7	3	2	-3	0	-1	0
35 g[a] MMTT	LY900014	14 (8 – 22)	27 (18 – 38)	55 (42 – 69)	70 (55 – 85)	28 (19 - 38)	10 (4 – 16)	5 (1 – 9)	9 (4 – 16)
	Humalog	13 (6 – 21)	20 (12 – 28)	44 (33 – 57)	67 (52 – 82)	25 (16 – 34)	14 (7 – 22)	8 (3 – 15)	9 (4 – 15)
	RR	1.08	1.35	1.25	1.04	1.12	0.71	0.62	1.00
	RD	1	7	11	3	3	-4	-3	0
15 g[a] MMTT	LY900014	11 (5 – 18)	26 (17 – 37)	58 (46 – 73)	82 (67 – 99)	32 (22 – 43)	13 (6 – 20)	11 (5 - 18)	13 (7 – 20)
	Humalog	10 (4 – 16)	20 (12 – 29)	45 (33 – 58)	74 (59 – 88)	25 (17 – 34)	15 (8 – 23)	13 (7 – 20)	14 (8 – 22)
	RR	1.10	1.30	1.29	1.11	1.28	0.87	0.85	0.93
	RD	1	6	13	8	7	-2	-2	-1

Abbreviations: 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 IR response on 7/15/2022. Table 5.2

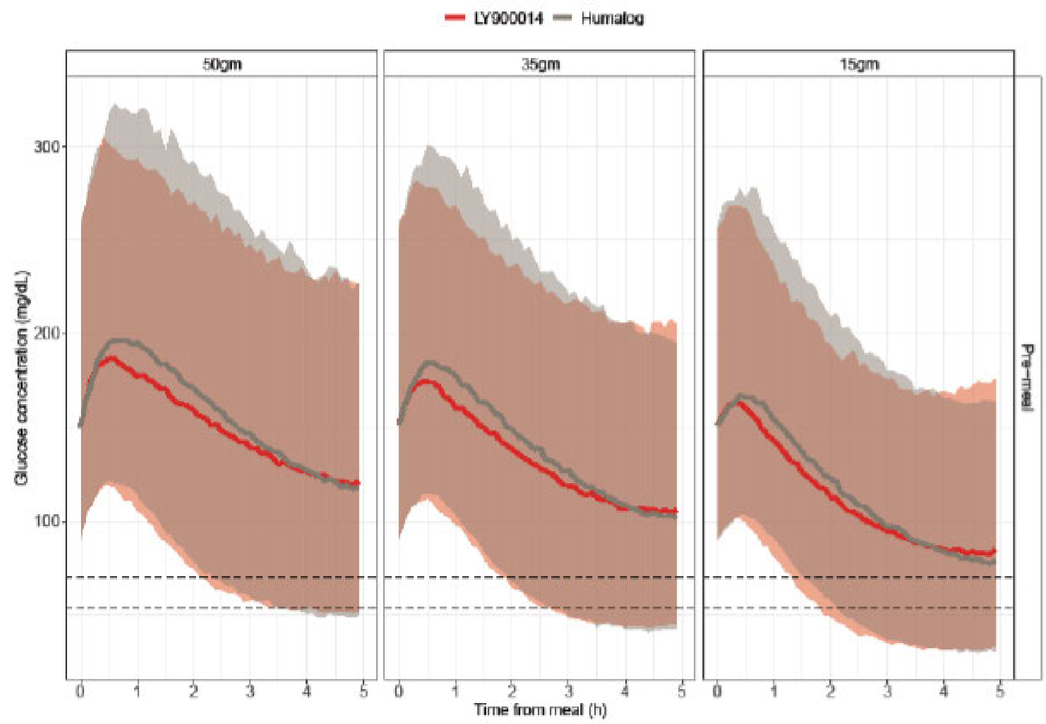
T2DM

The distribution of model-predicted PPG over time for children with T2DM given an MMTT containing 1) 50 g, 2) 35 g, or 3) 15 g of carbohydrates with LY900014 or Humalog administered prior to the start of the meal is shown in ***Figure 15***. The simulations incorporated the same insulin dose amounts and showed that the median and range of PPG decreased as the carbohydrate amount in MMTT decreased from 50 to 15 g for both LY900014 and Humalog treatment given prior to the start of the meal. The LY900014 treatment group showed a lower glucose excursion compared to Humalog across all simulated carbohydrate amounts.

Summaries of the number of simulated BG ≤70 or BG ≤54 mg/dL at ≤0.5, ≤1, ≤2, ≤4, >1 to ≤2, >2 to ≤3, >3 to ≤4, and >4 to ≤5 hours following administration of MMTT containing 50, 35, or 15 g of carbohydrates in children with T2DM given LY900014 or Humalog prior to the start of the MMTT are shown in ***Figure 16***, ***Table 11***, and ***Table 12***.

A higher incidence of hypoglycemia was demonstrated in the simulations as the carbohydrate amounts were reduced for the same insulin dose amount, as expected. The hypoglycemic events were generally low for both LY900014 and Humalog in the simulation. The range of simulated number of events for BG ≤70 or BG ≤54 mg/dL over the duration of the MMTT overlaps for each timing and carbohydrate amount. The RR and RD of LY900014 and Humalog were generally consistent across carbohydrate amounts.

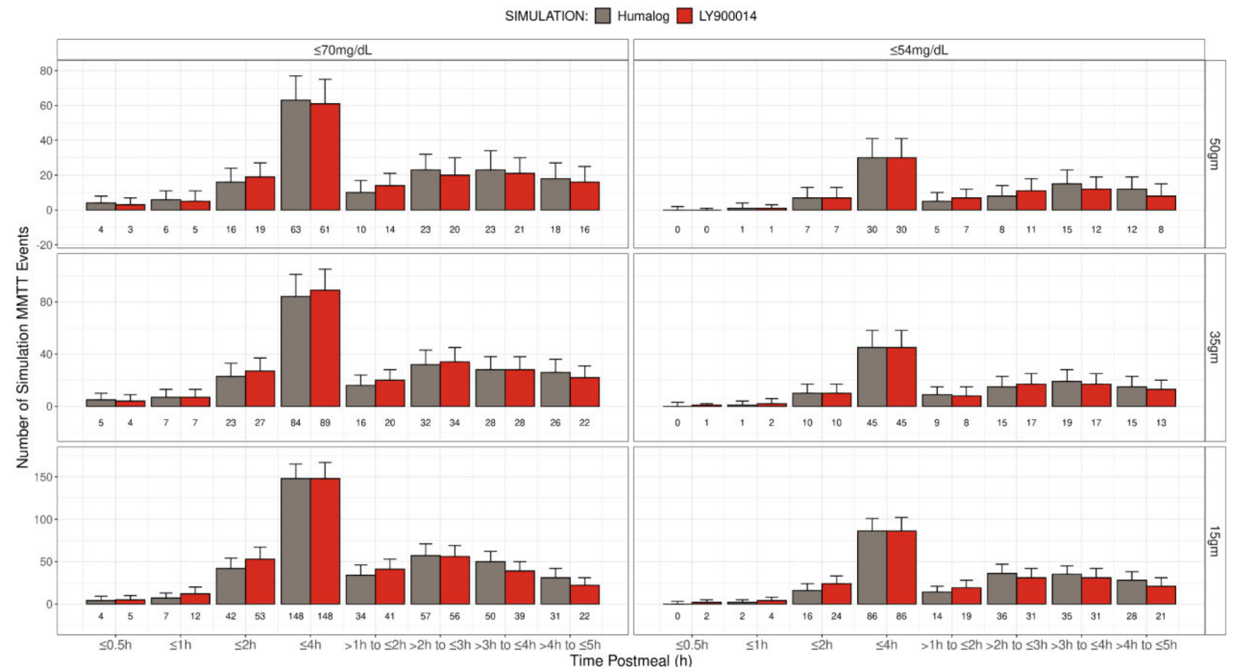
Figure 15. Model-predicted glucose time course in children with T2DM following an MMTT containing 50 g (left column), 35 g (middle column), or 15 g (right column) of carbohydrate and LY900014 or Humalog given immediately before the start of the meal.



Abbreviations: IGI = integrated glucose-insulin; MMTT = mixed meal tolerance test; PI = prediction interval; T2DM = type 2 diabetes mellitus. Note: The solid lines represent the median of the simulation based on the T2DM IGI model and the shaded area denotes the 90% PI.

Source: Applicant's IR response on 7/15/2022. Table 5.3

Figure 16. Model-predicted glucose ≤70 mg/dL (left column) or ≤54 mg/dL (right column) in children with T2DM following the MMTT containing 50 g (top row), 35 g (middle row), or 15 g (bottom row) of carbohydrates and LY900014 or Humalog given immediately before the meal



Abbreviations: MMTT = mixed meal tolerance test; T2DM = type 2 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 IR response on 7/15/2022. Table 5.4

Table 11. Comparison of Model-Predicted Glucose ≤70 mg/dL in Children with T2DM Given Either LY900014 or Humalog Prior to the Start of MMTT

		Number of glucose ≤70 mg/dL							
Simulations of		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤3 h	>3 to ≤4 h	>4 to ≤5 h
50 g[a] MMTT	LY900014	3 (0 – 7)	5 (1 – 11)	19 (12 – 27)	61 (48 – 75)	14 (7 – 21)	20 (13 – 30)	21 (13 – 30)	16 (10 – 25)
	Humalog	4 (0 – 8)	6 (2 – 11)	16 (9 – 24)	63 (50 – 77)	10 (5 – 17)	23 (14 - 32)	23 (15 – 34)	18 (11 – 27)
	RR	0.75	0.83	1.19	0.97	1.40	0.87	0.91	0.89
	RD	-1	-1	3	-2	4	-3	-2	-2
35 g[a] MMTT	LY900014	4 (1 – 9)	7 (2 – 13)	27 (18 – 37)	89 (74 – 105)	20 (12 - 28)	34 (23 – 45)	28 (19 – 38)	22 (13 – 31)
	Humalog	5 (1 – 10)	7 (3 – 13)	23 (15 – 33)	84 (70 – 101)	16 (9 – 24)	32 (23 – 43)	28 (18 – 38)	26 (17 – 36)
	RR	0.80	1.00	1.17	1.06	1.25	1.06	1.00	0.85
	RD	-1	0	4	5	4	2	0	-4
15 g[a] MMTT	LY900014	5 (1 – 10)	12 (6 – 20)	53 (40 – 67)	148 (130 – 167)	41 (29 – 53)	56 (44 – 69)	39 (28 – 50)	22 (14 – 31)
	Humalog	4 (1 – 9)	7 (3 – 13)	42 (30 – 54)	148 (132 – 165)	34 (23 – 46)	57 (44 – 71)	50 (39 – 62)	31 (21 – 42)
	RR	1.25	1.71	1.26	1.00	1.21	0.98	0.78	0.71
	RD	1	5	11	0	7	-1	-11	-9

Abbreviations: 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 IR response on 7/15/2022. Table 5.3

Table 12. Comparison of Model-Predicted Glucose ≤54 mg/dL in Children with T2DM Given Either LY900014 or Humalog Prior to the Start of MMTT

Simulations of		Number of glucose ≤54 mg/dL							
		≤0.5 h	≤1 h	≤2 h	≤4 h	>1 to ≤2 h	>2 to ≤3 h	>3 to ≤4 h	>4 to ≤5 h
50 g[a] MMTT	LY900014	0 (0 – 1)	1 (0 – 3)	7 (3 – 13)	30 (21 – 41)	7 (2 – 12)	11 (5 – 18)	12 (6 – 19)	8 (3 – 15)
	Humalog	0 (0 – 2)	1 (0 – 4)	7 (2 – 13)	30 (21 – 41)	5 (1 – 10)	8 (3 - 14)	15 (8 – 23)	12 (6 – 19)
	RR	0	1.00	1.00	1.00	1.40	1.38	0.80	0.67
	RD	0	0	0	0	2	3	-3	-4
35 g[a] MMTT	LY900014	1 (0 - 2)	2 (0 – 6)	10 (5 – 17)	45 (33 – 58)	8 (3 - 15)	17 (10 – 25)	17 (10 – 25)	13 (7 – 20)
	Humalog	0 (0 – 3)	1 (0 – 4)	10 (5 – 17)	45 (34 – 58)	9 (4 – 15)	15 (8 – 23)	19 (11 – 28)	15 (9 – 23)
	RR	1.00	2.00	1.00	1.00	0.89	1.13	0.89	0.87
	RD	1	1	0	0	-1	2	-2	-2
15 g[a] MMTT	LY900014	2 (0 – 5)	4 (1 – 8)	24 (14 – 33)	86 (70 – 102)	19 (11 – 28)	31 (21 – 42)	31 (21 – 42)	21 (13 – 31)
	Humalog	0 (0 – 3)	2 (0 – 5)	16 (8 – 24)	86 (72 – 101)	14 (7 – 21)	36 (25 – 47)	35 (24 – 45)	28 (19 – 38)
	RR	2.00	2.00	1.50	1.00	1.36	0.86	0.89	0.75
	RD	2	2	8	0	5	-5	-4	-7

Abbreviations: 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 IR response on 7/15/2022. Table 5.4

Table 13. Comparison of Observed and Model-Predicted Relative Risk of Hypoglycemia between LY900014 to Humalog in Children with T1DM

Overall Observed Hypoglycemia during 26-Week Treatment Period of Study ITSB					
		≤54 mg/dL		≤70 mg/dL	
Documented Hypoglycemia	Observed pediatric data in ITSB	RR	95% CI	RR	95% CI
		0.96	0.78-1.19	0.96	0.82-1.13
Observed Postmeal Hypoglycemia in Study ITSB and Simulated Postmeal Hypoglycemia by Time Interval					
Time Interval		≤54 mg/dL		≤70 mg/dL	
		RR	95% CI	RR	95% CI
≤1 hour	Observed pediatric data in ITSB	1.28	0.86-1.92	1.29	0.88-1.90
	Simulations with 50 g	1.47	0.41-2.69	1.14	0.71-1.64
	Simulations with 35 g	1.35	0.55-2.37	1.20	0.79-1.64
	Simulations with 15 g	1.30	0.55-2.24	1.16	0.77-1.58
≤2 hours	Observed pediatric data in ITSB	1.33	1.02-1.72	1.25	0.99-1.56
	Simulations with 50 g	1.08	0.64-1.57	1.03	0.74-1.34
	Simulations with 35 g	1.25	0.77-1.78	1.19	0.88-1.52
	Simulations with 15 g	1.29	0.86-1.78	1.10	0.84-1.38
≤4 hours	Observed pediatric data in ITSB	1.09	0.87-1.36	1.03	0.86-1.24
	Simulations with 50 g	1.04	0.67-1.41	0.97	0.73-1.22
	Simulations with 35 g	1.04	0.72-1.40	1.10	0.86-1.35
	Simulations with 15 g	1.11	0.83-1.43	1.04	0.86-1.23
≥4 hours	Observed pediatric data in ITSB	0.74	0.53-1.03	0.79	0.64-0.98
	Simulations with 50 g	1.00	0.00-3.34	0.62	0.00-1.94
	Simulations with 35 g	1.00	0.00-2.69	1.27	0.03-2.72
	Simulations with 15 g	0.93	0.16-1.79	0.94	0.26-1.79

Abbreviations: CI = confidence interval; RR = relative ratio calculated using LY900014 median number of events divided by Humalog median number of events; T1DM = type 1 diabetes mellitus.

Source: Applicant's IR response on 7/15/2022. Table 5.5

4.3.2.2.3.3.1. Reviewer's Comments and Analysis

Consistent with the observations in adults, the model-predicted glucose time course profiles showed that LY900014 has a greater glucose-lowering effect than Humalog in children with T1DM or T2DM, independent of the carbohydrate amount in the MMTT. As expected, the model-predicted glucose time course profiles showed that the risk of hypoglycemia increased for both LY900014 and Humalog as the amount of carbohydrates within the MMTT decreased while maintaining the same insulin dose.

A slightly greater number of hypoglycemic events was observed in the early postprandial period while fewer occurred at the end of the postprandial period with LY900014 as compared to Humalog, which aligns with the faster time-action profile of LY900014, as well as observations from ITSB studies.

The Applicant's analyses did not investigate impact of age/body weight on the hypoglycemia risks for kids. Therefore, reviewer conducted additional analyses for subjects ≤ 26 kg versus > 26 kg subgroups for the body weight effects. The reason we use 26 kg as the cut-off is because according to the CDC growth chart, 95% of children less than 26 kg are younger than 6 years of age. In addition, the percentage of patients with hypoglycemia events within the time interval was calculated and used as the y axis, allowing comparison across different body weight and age subgroups.

Since the simulated population used a fixed dose of 10 U for all subjects, subjects with lower body weight (≤ 26 kg, mean at 0.45 U/kg) had higher dose (**Figure 17**) than subjects with higher body weight (> 26 kg, mean at 0.26 U/kg). The dose for lower body weight subgroup is also higher than that tested in Study ITSA (0.2U/kg), therefore the simulation for hypoglycemia risks were more conservative than the conditions in Study ITSA.

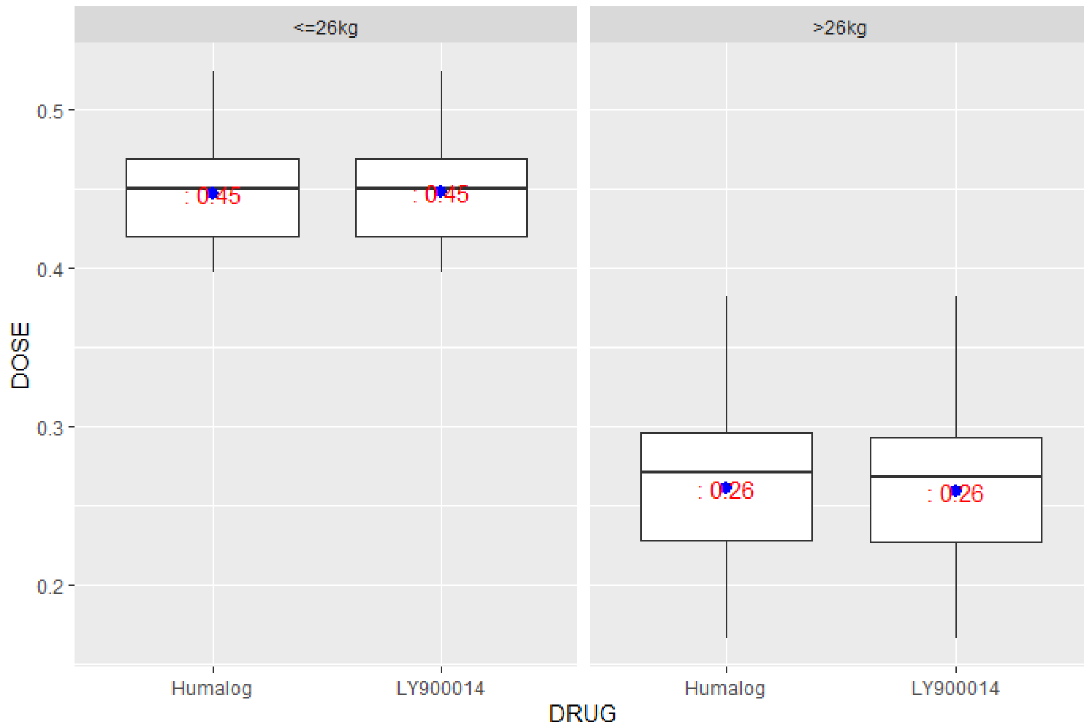
The resulted showed that model-predicted glucose time course in children with T1DM and T2DM were similar between lower body weight group (≤ 26 kg) and higher body weight groups (> 26 kg) among three MMTT conditions (**Figure 18**). Also, the model-predicted glucose time profiles are similar between LY900014 and Humalog under these conditions (**Figure 18**).

For patients with T1DM, hypoglycemia risks (≤ 70 mg/dL or ≤ 54 mg/dL) was predicted to be higher in patients with higher body weight (> 26 kg) than those with a lower body weight (≤ 26 kg) among all three MITT conditions. While the hypoglycemia risks (≤ 70 mg/dL or ≤ 54 mg/dL) were comparable between LY900014 and Humalog treatment groups.

Similarly, for patients with T2DM, hypoglycemia risks (≤ 70 mg/dL or ≤ 54 mg/dL) was predicted to be higher in patients with higher body weight (> 26 kg) than those with a lower body weight (≤ 26 kg) among all three MITT conditions. While the hypoglycemia risks (≤ 70 mg/dL or ≤ 54 mg/dL) were comparable between LY900014 and Humalog treatment groups.

Since the simulated dose was higher for younger children with lower body weight than those for older children with higher body weight, this result suggests that the hypoglycemia risk for younger children with lower body weight is not likely to be higher than the older children with higher body weight even at relatively higher dose.

Figure 17. Box plots of dose levels for the simulated population by body weight groups and treatments.

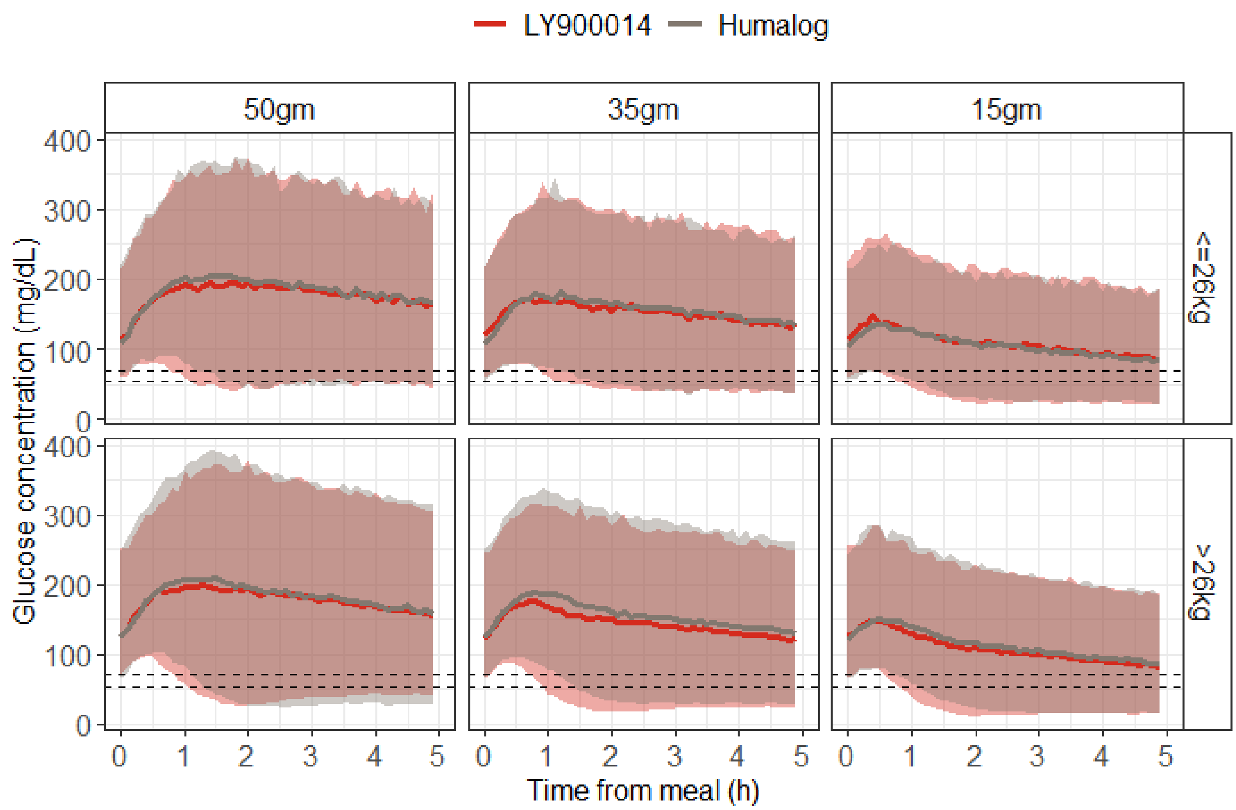


Dose: Unite/kg

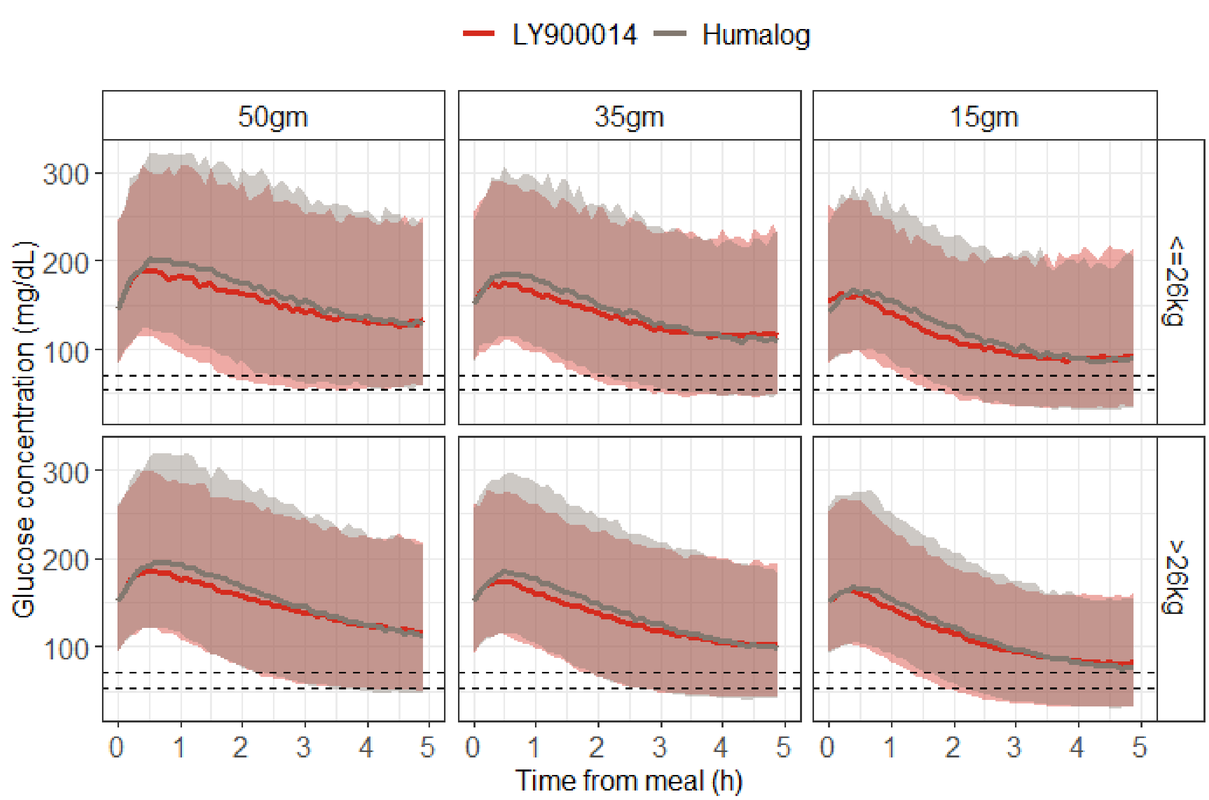
Source: reviewer's analyses

Figure 18. Model-predicted glucose time course in children with T1DM and T2DM following an MMTT containing 50 g (left column), 35 g (middle column), or 15 g (right column) of carbohydrate and LY900014 or Humalog given immediately before the start of the meal by body weight groups (≤ 26 kg versus > 26 kg).

T1DM


LY900014
Humalog
50gm
35gm
15gm
Glucose concentration (mg/dL)
400
300
200
100
0
<=26kg
>26kg
0 1 2 3 4 5
Time from meal (h)

T2DM

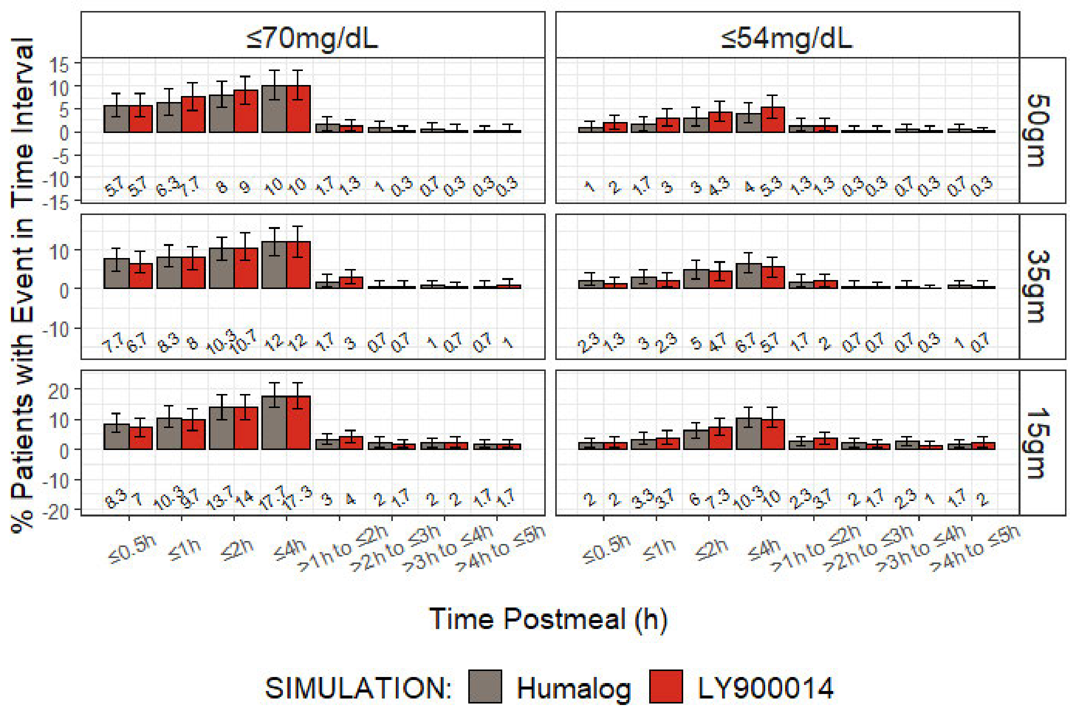

LY900014
Humalog
50gm
35gm
15gm
Glucose concentration (mg/dL)
300
200
100
<=26kg
>26kg
0 1 2 3 4 5
Time from meal (h)

Source: reviewer's analyses

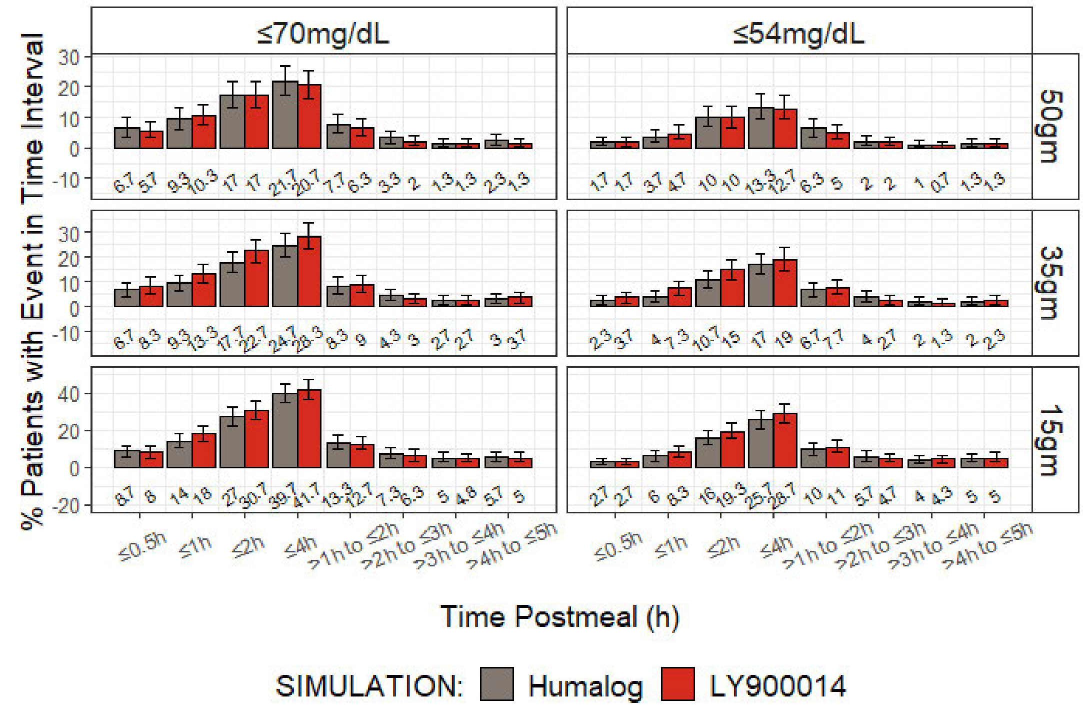
T1DM

Figure 19. Model-predicted glucose ≤70 mg/dL (left column) or ≤54 mg/dL (right column) in children with T1DM following the MMTT containing 50 g (top row), 35 g (middle row), or 15 g (bottom row) of carbohydrates and LY900014 or Humalog given immediately before the meal by body weight groups (≤ 26 kg versus > 26 kg).

≤26 kg



> 26 kg

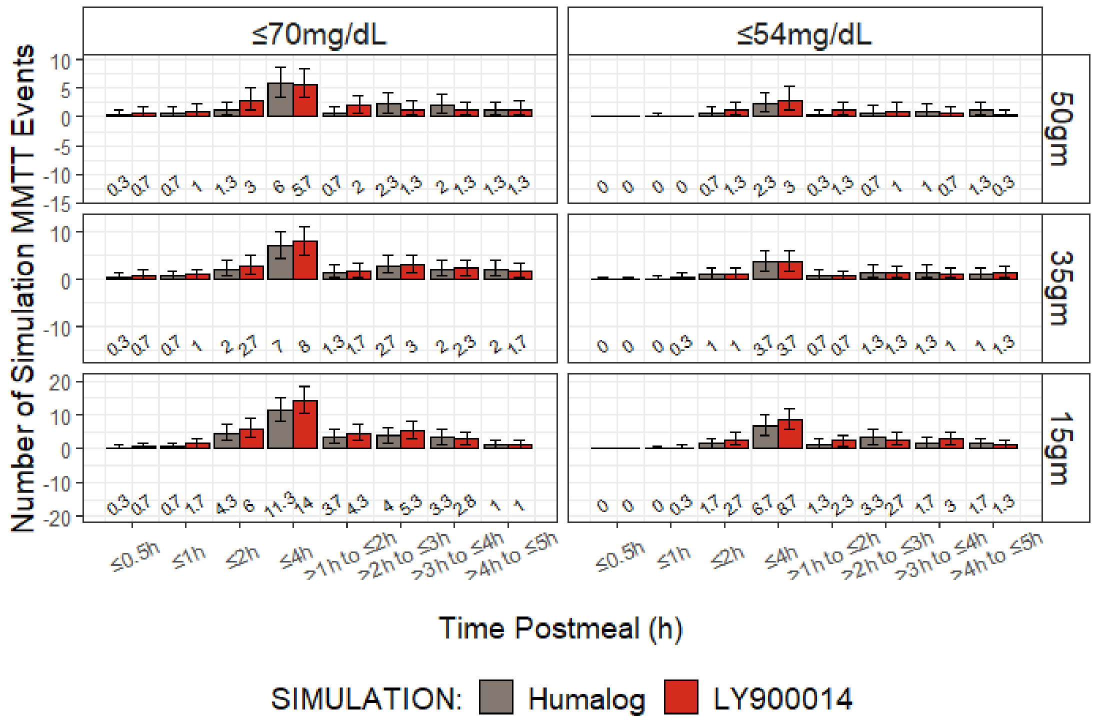


Source: reviewer's analyses.

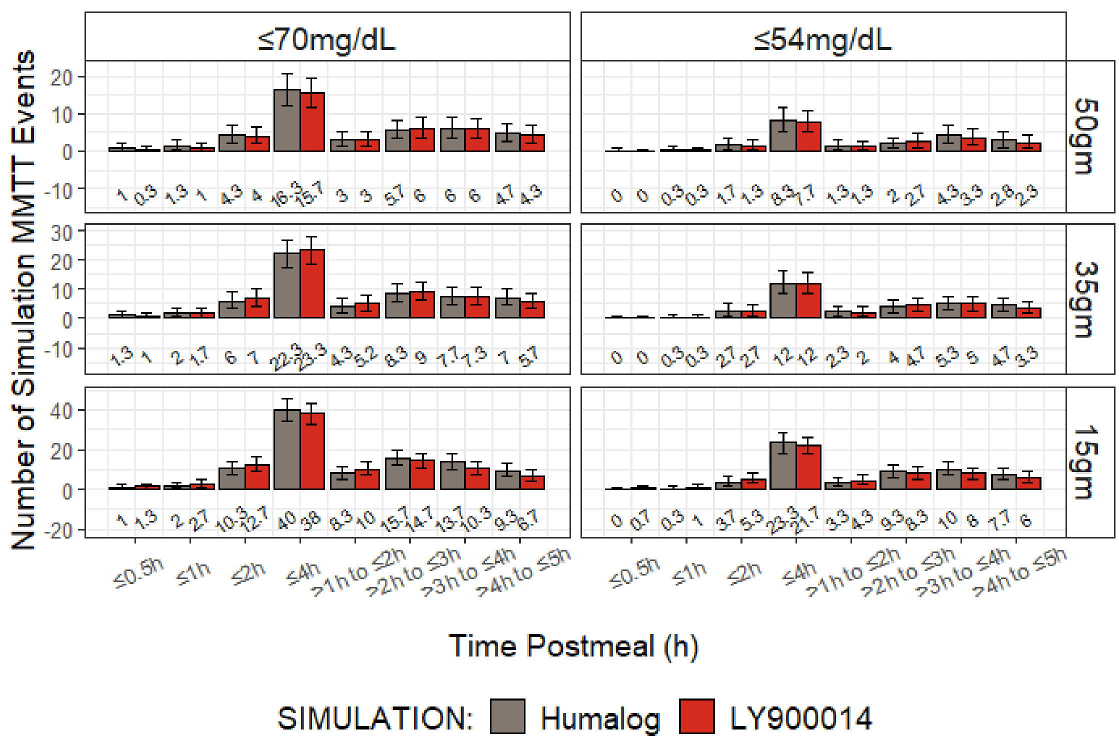
T2DM

Figure 20. Model-predicted glucose ≤70 mg/dL (left column) or ≤54 mg/dL (right column) in children with T2DM following the MMTT containing 50 g (top row), 35 g (middle row), or 15 g (bottom row) of carbohydrates and LY900014 or Humalog given immediately before the meal by body weight groups (≤ 26 kg versus > 26 kg).

≤ 26 kg



> 26 kg



Source: reviewer's analyses.

4.3.3. Conclusions

Based on the final optimized population PK model of insulin lispro and PK/PD model of the PPG data following MMTT in children, adolescents, and adults with T1DM on MDI and CSII therapy, the following objectives were addressed by the analyses:

- Characterize the PK of insulin lispro following SC injection of either LY900014 or Humalog in pediatric patients with T1DM on MDI and CSII therapies (refer to Section 0)
  - The optimized adult/pediatric PopPK model for MDI and CSII therapy could well described the pharmacokinetic profiles of LY900014 and Humalog in children, adolescents and adults with T1DM following MDI and CSII therapy in Study ITSA.
  - Body weight was included as a covariate on all clearance and volume parameters in the final adult/pediatric PopPK model. Although body weight was a significant covariate, adjustment of LY900014 dose should be based on the clinical response of the individual and no dose adjustment is needed due to body weight, as with all other insulin products.
  - From the model simulation, LY900014 showed an accelerated insulin lispro absorption with a reduction in late insulin exposure compared with Humalog across all 3 age groups via either MDI or CSII therapies.
- Predict the PK of insulin lispro following SC injection of either LY900014 or Humalog in pediatric patients with T2DM (refer to Section 0)
  - The adult T2D PopPK model was adjusted based on the changes made between the adult PopPK model in patients with T1D and the final optimized PK/PD model for adult, children, and adolescents with T1D in Study ITSA.
  - The model-predicted insulin lispro PK profiles in children and adolescents with T2DM showed an accelerated absorption and a reduction in the late insulin exposure with LY900014 compared to Humalog as observed in adults with T2DM.
- Characterize the exposure-response relationship between insulin lispro concentration and PPG lowering following SC injection of either LY900014 or Humalog in pediatric patients with T1DM via MDI or CSII therapy (refer to Section 0)
  - The IGI model describing the relationship between the PPG and insulin lispro PK following LY900014 and Humalog in adult/pediatric patients with T1D were optimized using ITSA data.
  - The PK/PD model confirmed that the differences in the time course of insulin lispro concentration for LY900014 and Humalog described the differences in the observed PPG response in pediatric patients with T1D on MDI or CSII therapy.
  - The model confirmed that the same PK/PD relationship was maintained, independent of study population (adult or pediatric) or whether LY900014 or Humalog was given as MDI or CSII therapy.
- Predict the PPG response post-meal a test meal following SC injection of either LY900014 or Humalog in pediatric patients with T1DM (refer to Section 0)
  - When both insulins (LY900014 and Humalog) were given prior to the start of the meal or 20 minutes after the start of the meal, the model-predicted glucose profiles show a

greater glucose-lowering effect with LY900014 than Humalog in children, adolescents, and adults with T2DM.

- Predict the PPG response during a test meal following SC injection of either LY900014 or Humalog in pediatric patients with T2DM (refer to Section 0)
  - When both insulins (LY900014 and Humalog) were given prior to the start of the meal or 20 minutes after the start of the meal, the model-predicted glucose profiles show a greater glucose-lowering effect with LY900014 than Humalog in children, adolescents, and adults with T2DM. There is not a higher hypoglycemia risk for LY900014 as compared to Humalog administered during a test meal following SC injection in patients with T2DM across three age groups. Therefore, PK/PD simulations supported that administer LY900014 in pediatric patients with T2DM is acceptable.
- Conducting simulations to prediction hypoglycemia risks down to 4 years of age (refer to Section 0).
  - Simulations were conducted in pediatric patients (4 to 12 years of age) with T1DM and T2DM following a fixed dose of 10 U of LY900014 or Humalog administered prior to the start of the meal based on different MMTT (50, 35, or 15 g of carbohydrate). The percentage of subjects with reported hypoglycemia events (BG ≤70 or BG ≤54 mg/dL) were tabulated at different time intervals (≤0.5, ≤1, ≤2, ≤4, >1 to ≤2, >2 to ≤3, >3 to ≤4, and >4 to ≤5 hours).
  - The results showed that a higher incidence of hypoglycemia was demonstrated as the carbohydrate amounts were reduced for the same insulin dose amount across different age groups, as expected. The relative risk (RR) and relative difference (RD) of LY900014 to Humalog were generally consistent across carbohydrate amounts.
  - Younger children with body weight ≤ 26 kg were shown to have less hypoglycemia risks as compared to older children with body weight > 26 kg, although simulated at relatively higher dose levels.

4.3.4. Listing of analyses codes and output files

PopPK models

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the final T1DM PK model for children, adolescents, and adults via MDI therapy	URLI_ITSA_v3.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\ Code\PopPK\Dataset\ITSA partA
NONMEM code for the final T1DM PK model for children, adolescents, and adults via MDI therapy	run30.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\ Code\PopPK\Dataset\ITSA partA

NONMEM dataset for the final T1DM PK model for children, adolescents, and adults via CSII therapy	URLI_ITSA_B_v3.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PopPK\Dataset\ITSA partB
NONMEM code for the final T1DM PK model for children, adolescents, and adults via CSII therapy	run42.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PopPK\Dataset\ITSA partB
MDI: PK Simulation Dataset for T2DM for Study ITSA (Children, Adolescents, and Adults) Part A	URLI_ITSA_v3_T2.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PopPK\Dataset\Simulation T2D
MDI: PK Simulation NONMEM code for T2DM for Study ITSA (Children, Adolescents, and Adults) Part A	run200.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PopPK\Dataset\Simulation T2D

PK/PD models

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the final T1DM IGI model for children, adolescents, and adults via MDI	ITSA_PKPD_T1_v1.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\ITSA partA
NONMEM code for the final T1DM IGI model for children, adolescents, and adults via MDI from Study ITSA Part A	run45.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\ITSA partA
NONMEM dataset for the final T1DM IGI model for children, adolescents, and adults via CSII	ITSA_PKPD_B_v3.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\ITSA partB

NONMEM code for the final T1DM IGI model for adolescents and adults via CSII	run46.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\ITSA partB
MDI: IGI Simulation Dataset for T2DM for Study ITSA (Children Adolescents, and Adults) prior to the meal	ITSA_PKPD_T2_V 1.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\Simulation
MDI: IGI Simulation NONMEM code for T2DM for Study ITSA (Children Adolescents, and Adults) via MDI therapy prior to the meal	run8.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\Simulation
MDI: IGI Simulation Dataset for T2DM for Study ITSA (Adolescents, and Adults) 20 minutes after the meal	ITSA_PKPD_T2_V 1.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\Simulation
MDI: IGI Simulation NONMEM code for T2DM for Study ITSA (Adolescents, and Adults) via MDI therapy 20 minutes after the meal	run9.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\PKPD\Simulation

Simulation for Children down to 4 years of age with different body weight and MMTT plans (15g, 35g, or 50 g)

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Simulation T1DM dataset for LY900014 and Humalog with Carbohydrates=50g	simulation_id_36796.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t1dm

Simulation T1DM dataset for LY900014 and Humalog with Carbohydrates=35g	simulation_id_36831.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t1dm
Simulation T1DM dataset for LY900014 and Humalog with Carbohydrates=15g	simulation_id_36832.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t1dm
R script and .csv output tabulating the simulated hypoglycemia events for various scenarios for children in Studies ITSB and ITSA using the updated children integrated glucose-insulin T1DM PK/PD model.	muse-itsb-simulation-hypo-t1 r muse_itsb_simulation_mmtt_trials-1000_t1.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t1dm
R script for plotting the bar plots of simulated hypoglycemia events under various scenarios for children in Studies ITSB and ITSA using the updated children integrated glucose-insulin T1DM PK/PD model.	muse-t1d-children-simulation-hypo-plotting-final r	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t1dm
Reviewer's analyses for tabulating and plotting the simulated hypoglycemia events for various scenarios for children (≤ 26 kg versus > 26 kg) in Studies ITSB and ITSA using the updated children integrated glucose-insulin T1DM PK/PD model	muse-itsb-simulation-hypo-t1 r muse-t1d-children-simulation-hypo-plotting-final r	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\Reviewer's analysis\t1dm
Simulation T2DM dataset for LY900014 with carbohydrates=50g	simulation_id_36840.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm

Simulation dataset for Humalog with Carbohydrates=50g	simulation_id_36841.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm
Simulation dataset for LY900014 with Carbohydrates=35g	simulation_id_36842.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm
Simulation dataset for Humalog with Carbohydrates=35g	simulation_id_36843.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm
Simulation dataset for LY900014 with Carbohydrates=15g	simulation_id_36844.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm
Simulation dataset for Humalog with Carbohydrates=15g.	simulation_id_36845.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm
R script and .csv output tabulating the simulated hypoglycemia events for various scenarios for children in Studies ITSB and ITSA using the updated children integrated glucose-insulin T2DM PK/PD model.	muse-itsb-simulation-hypo-t2 r muse-itsb-simulation-mmtt-trials-1000-t2.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm
R script for plotting the bar plots of simulated hypoglycemia events under various scenarios for children in Studies ITSB and ITSA using the updated children integrated glucose-insulin T2DM PK/PD model.	muse-t2d-children-simulation-hypo-plotting.r	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\t2dm
Reviewer's analyses for tabulating and plotting the simulated hypoglycemia events for various scenarios	muse-itsb-simulation-hypo-t2 r muse-t2d-children-simulation-hypo-plotting.r	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lyumjev_BLA 761109_XP\Code\Simulation down to 4 years of age\Reviewer's analysis\t2dm

for children (≤ 26 kg versus > 26 kg) in Studies ITSB and ITSA using the updated children integrated glucose-insulin T2DM PK/PD model		

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