CLINICAL REVIEW

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Division/Office	Division of Diabetes, Lipid Disorders and Obesity (DDLO) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Reviewer Name(s)	Dolly Misra, MD
Review Completion Date	October 7, 2022
Established/Proper Name	Insulin lispro-aabc
(Proposed) Trade Name	Lyumjev
Applicant	Eli Lilly and Company
Dosage Form(s)	100 units/mL in 10 mL vial, 3 mL cartridge, 3 mL pre-filled pen 200 units/mL in 3 mL pre-filled pen
Applicant Proposed Dosing Regimen(s)	Individualized titration for glycemic control
Applicant Proposed Indication(s)/Population(s)	To improve glycemic control in adult and pediatric patients with diabetes mellitus
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult and pediatric patients with diabetes mellitus

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Glossary

AC	advisory committee
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
AR	adverse reaction
β-cell	beta cell
BG	blood glucose
BID	twice daily
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMQ	customized MedDRA query
CRF	case report form
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	Coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSII	continuous subcutaneous insulin infusion
CSR	clinical study report
DKA	diabetic ketoacidosis
ECG	electrocardiogram
eCTD	electronic common technical document
EOP2	end of phase 2
ETASU	elements to assure safe use
FCDP	fixed combination dose product
FDA	Food and Drug Administration

FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FGM	flash glucose monitoring
GCP	good clinical practice
GD	glucodynamic
HbA1c	hemoglobin A1c
ICH	International Council for Harmonization
ICR	insulin to carbohydrate ratio
IND	Investigational New Drug Application
IP	investigational product
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intention-to-treat
IV	intravenous
MDI	multiple daily injection
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMTT	mixed-meal tolerance test
Nab	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NIM	non-inferiority margin
NME	new molecular entity
OAM	oral anti-hyperglycemic medication
OBP	Office of Biotechnology Products
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPG	postprandial glucose
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

PSUR	Periodic Safety Update report
PT	preferred term
QD	once daily
REMS	risk evaluation and mitigation strategy
RR	relative rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SMBG	self-monitored blood glucose
SMQ	Standardized MedDRA Query
SOC	system organ class
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
TEADA	treatment emergent anti-lispro antibody
TEAE	treatment emergent adverse event
TIR	time in range
U.S.	United States
WRO	Written response only

1. Executive Summary

1.1. Product Introduction

Lyumjev (insulin lispro-aabc) is a rapid-acting human insulin analog manufactured by Eli Lilly and Company (Applicant) approved for subcutaneous (SC) delivery via multiple daily injections (MDI), continuous subcutaneous insulin infusion (CSII), and intravenous (IV) administration for the improvement of glycemic control in adult patients with diabetes in the Unites States (U.S.). Insulin lispro products differ from human insulin by the substitution of the amino acid proline at position B28 for lysine and the replacement of lysine in position B29 by proline. Lyumjev differs from other insulin lispro formulations in that it includes (b) (4) treprostinil (b) (4) and sodium citrate (b) (4)

The primary activity of Lyumjev is the regulation of glucose metabolism. Insulins exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis and enhance protein synthesis.

The Biologics License Application (BLA) for Lyumjev 100 units/mL and 200 units/mL (BLA 761109) received Food and Drug Administration (FDA) approval on June 15, 2020. Both concentrations are approved for SC administration via MDI. Lyumjev 100 unit/mL is also approved for IV administration, and the CSII condition of use for Lyumjev 100 unit/mL was approved August 13, 2021.

The Applicant has submitted this supplemental BLA (sBLA) for Lyumjev to expand the indication to pediatric patients with diabetes mellitus and add CSII as a condition of use in the pediatric population. To support the use of Lyumjev in this younger age group, this submission includes new clinical data from a pivotal phase 3 safety and efficacy trial, I8B-MC-ITSB (ITSB), conducted to satisfy postmarketing requirement (PMR 3874-1) under the Pediatric Research Equity Act (PREA), and from a phase 1 clinical pharmacology study, I8B-MC-ITSA (ITSA). The Applicant has additionally provided findings from pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation to further support the use of Lyumjev in the diabetic pediatric patient population.

The Applicant's product code name for Lyumjev (insulin lispro-aabc) during its development program is LY900014, and it is used interchangeably with Lyumjev in this review. The clinical data in this submission, including tabular and graphical presentations, predominantly refer to Lyumjev as LY900014.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I recommend approval of BLA 761109/S-004. My recommendation is consistent with those of all other review disciplines for the supplement.

To support the use of LY900014 in the pediatric population with diabetes mellitus, this submission includes new clinical data from the pivotal phase 3 safety and efficacy trial, Study ITSB, which was conducted to fulfill PMR 3874-1: *Conduct a 26-week, randomized, controlled efficacy and safety study comparing Lyumjev (insulin lispro-aabc) administered at mealtime and Lyumjev (insulin lispro-aabc) administered 20 minutes postmeal to Humalog administered at mealtime, in combination with long acting insulin, in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive).*

Study ITSB was a 26-week, randomized, active controlled, treat-to-target, multinational trial that evaluated the efficacy of LY900014 in 716 pediatric patients with T1D. The primary objective of the study was to establish that LY900014 is noninferior to Humalog on glycemic control, as assessed by HbA1c, in patients 1 to < 18 years of age with T1D when administered as mealtime insulin in combination with basal insulin as part of an MDI regimen for 26 weeks. The prespecified noninferiority margin (NIM) was 0.4%. Multiplicity-adjusted objectives were to demonstrate noninferiority of LY900014 to Humalog on glycemic control when LY900014 is administered 20 minutes after the start of a meal and superiority of LY900014 to Humalog on glycemic when administered as mealtime insulin.

Study ITSB met its primary objective: the estimated treatment difference (LY900014 – Humalog) for reduction in HbA1c from baseline to week 26 was -0.01 (95% CI: -0.15, 0.14), establishing noninferiority of LY900014 to Humalog as the upper bound of the two-sided 95% CI for treatment difference was less than the prespecified NIM of 0.4%. Similarly, Study ITSB met its first multiplicity adjusted secondary objective of demonstrating noninferiority of LY+20 to Humalog with and estimated treatment difference (LY+20 – Humalog) of 0.00 (95% CI: -0.18, 0.18). The superiority of mealtime LY900014 to Humalog was not achieved because the upper bound of the 95% CI was above 0. The results of the primary analyses were corroborated by the FDA statistical reviewer and were robust to sensitivity analysis using alternative missing data assumptions. In addition, the analyses of changes in insulin doses between treatment arms over the treatment period did not show any statistically significant or clinically meaningful differences.

Study ITSA was a phase 1, randomized, double-blind, 2-period crossover study which compared the PK and PD profiles during a test meal of LY900014 and Humalog following SC administration of 0.2 U/kg in children (6 to <12 years), adolescents (12 to < 18 years) and adults (18 to <65 years) with T1D. In Part A of the study, patients received a single dose of LY900014 and

Humalog on 1 occasion each as SC bolus injection, and in Part B, patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus infusion via CSII.

Study ITSA demonstrated that the differences in PK profiles between LY900014 and Humalog following SC administration (via injection or via CSII bolus infusion) are similar in pediatric patients with T1D and adults with T1D. In the context of the demonstrated efficacy of Lyumjev in the pediatric T1D population based on the data from Study ITSB, the data from Study ITSA support the extrapolation of the efficacy of CSII condition of use for LY900014 established from prior Study ITRO (the pivotal CSII trial in adults with T1D, reviewed in BLA 761109/S-003) to the pediatric T1D population.

To broaden the pediatric indication of LY900014 (including when administered by CSII) to include patients with T2D, the totality of data from the LY900014 clinical and PK/PD investigations in pediatric and adult patients with T1D and adults with T2D was used to characterize the PK of LY900014 and predict the efficacy in patients with pediatric T2D. In addition to the observed data from the individual studies, FDA considered model-predicted insulin lispro PK profiles for patients with T2D based on the results from those studies: the models support a conclusion that LY900014 exerts glucose lowering effect comparable to Humalog across all age groups of patients with T2D (children, adolescents, and adults). Altogether, these data support the efficacy of LY900014 in pediatric patients with T2D.

In summary, the clinical data package submitted with this sBLA supports the efficacy of LY900014 in the broad pediatric diabetes population (i.e., T1D and T2D) and the CSII condition of use. Thus, the Applicant's proposed indication for LY900014 (i.e., indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus) is supported by the information in this submission.

Benefit-Risk Integrated Assessment

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia and is increasingly common in the United States (U.S.). Type 1 diabetes (T1D) is caused by autoimmune destruction of pancreatic beta cells, resulting in insulin deficiency, and type 2 diabetes (T2D) is characterized by either insulin resistance or a deficiency of insulin. Both types of diabetes increase the risk for both microvascular and macrovascular complications. Treatment with insulin is required for patients with T1D, and insulin therapy is also often necessary to manage glycemia in patients with T2D when diet, lifestyle intervention, and other antihyperglycemic agents have failed. Despite the availability of a number of insulin products with various pharmacokinetic (PK) and pharmacodynamic (PD) profiles, many diabetic patients requiring insulin do not achieve their glycemic targets. As an alternative to basal-bolus therapy, which requires subcutaneous (SC) dosing of multiple daily injections (MDI), insulin may be administered as a continuous subcutaneous insulin infusion (CSII) with the use of an external insulin pump. CSII administration is limited to the use of rapid acting insulin analogs. The CSII condition of use offers greater individualization of insulin by allowing titration of dosing by smaller increments compared to MDI. The management of pediatric patients with diabetes is challenging due their often-unpredictable diet and activity schedules as well as by their increased insulin sensitivity. The approval of another rapid acting insulin analog with a different PK/PD profile for use with MDI and CSII provides another treatment option to the pediatric population with diabetes.

The Applicant has submitted a supplemental new biologics license application (sBLA) for Lyumjev (insulin lispro-aabc). Lyumjev, product code name LY900014, is an insulin lispro product (b) (4) Lyumjev is licensed for SC and intravenous (IV) use to improve glycemic control in adults with diabetes mellitus and is also approved for the continuous subcutaneous insulin infusion (CSII) condition of use.

The Applicant has submitted this sBLA for Lyumjev seeking to expand the indication to the pediatric population and to add CSII as a condition of use in the pediatric patients with diabetes mellitus. The submission contains the data of two clinical trials. Study ITSB is a pivotal phase 3 trial investigating the efficacy and safety of LY900014 in comparison to Humalog for glycemic control in pediatric patients with T1D. Study ITSB was conducted to fulfill a postmarketing requirement (PMR-3874-1) under the Pediatric Research and Equity Act (PREA). In addition, the data from a phase 1 trial, Study ITSA, are provided to support the CSII condition of use for pediatric patients and to allow the extrapolation of efficacy of LY900014 to pediatric patients with T2D. The Applicant has also submitted PK/PD modeling and simulation to support the use of LY900014 in pediatric patients with T2D.

Study ITSB was a 26-week, randomized, active controlled, treat-to-target, multinational trial that evaluated the efficacy of LY900014 in 716 pediatric patients with T1D. The primary objective of the study was to establish that LY900014 is noninferior to Humalog on glycemic control, as assessed by HbA1c, in patients 1 to < 18 years of age with T1D when administered as mealtime insulin in combination with basal insulin as part of an MDI regimen for 26 weeks. The prespecified noninferiority margin (NIM) was 0.4%. Multiplicity-adjusted objectives were to demonstrate noninferiority of LY900014 to Humalog on glycemic control when LY900014 is administered 20 minutes after the start of a meal and superiority of LY900014 to Humalog on glycemic when administered as mealtime insulin. Patients were randomized (2:2:1) to either blinded mealtime LY900014 (N=280), blinded mealtime Humalog (N=298), or open-label postmeal LY900014 (N=138), all in combination with basal insulin (insulin glargine, insulin degludec or insulin detemir). Stratification factors included the following: country; HbA1c at screening (≤8.0% vs >8.0%); type of basal insulin (insulin glargine, detemir, or degludec); and age group (1 to <12 years vs 12 to <18 years). Mealtime LY900014 or Humalog was injected 0 to 2 minutes before the meal, and postmeal LY900014 (LY+20) was injected 20 minutes after the start of the meal. The patients enrolled in Study ITSB had a mean age of 12 years; 53% were male, 91% were White, 1% were Black or African American; and 24% of the US subpopulation in this trial were Hispanic. The mean BMI was 20.5 kg/m^2, the mean duration of diabetes was 5 years, and the mean HbA_{1c} at baseline was 7.8%.

Study ITSB met its primary objective: the estimated treatment difference (LY900014 – Humalog) for reduction in HbA1c from baseline to week 26 was -0.01 (95% CI: -0.15, 0.14), establishing noninferiority of LY900014 to Humalog as the upper bound of the two-sided 95% confidence interval (CI) for treatment difference was less than the prespecified NIM of 0.4%. Similarly, Study ITSB met its first multiplicity adjusted secondary objective of demonstrating noninferiority of LY+20 to Humalog with and estimated treatment difference (LY+20 – Humalog) of 0.00 (95% CI: -0.18, 0.18). The superiority of mealtime LY900014 to Humalog was not achieved because the upper bound of the 95% CI was above 0. The results of the primary analyses were corroborated by the FDA statistical reviewer and were robust to sensitivity analysis using alternative missing data assumptions. Importantly, the analyses of changes in insulin doses between treatment arms over the treatment period did not show any statistically significant or clinically meaningful differences.

The results of Study ITSB provide evidence of efficacy in terms of change in HbA1c, which is considered a well-validated surrogate for the long-term microvascular complications of diabetes mellitus. The results of the Diabetes Control and Complications Trial (DCCT)[3-9] showed in that in T1D, lowering blood glucose (as measured by HbA1c) delayed the onset and slowed the progression of microvascular complications, namely retinopathy, nephropathy, and neuropathy. Similarly, the results of the Kumamoto Study[14] showed that intensive insulin therapy resulting in better glycemic control (HbA1c < 7.1%) prevents the progression of microvascular complications in patients with T2D.

Study ITSA was a phase 1, randomized, double-blind, 2-period crossover study which compared the pharmacokinetic (PK) and pharmacodynamic (PD) profiles during a test meal of LY900014 and Humalog following SC administration of 0.2 U/kg in children (6 to <12 years), adolescents (12 to < 18 years) and adults (18 to <65 years) with T1D. In Part A of the study, patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus injection, and in Part B, patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus infusion via CSII. A total of 41 out of 42 patients completed Part A, and 37 out of 39 randomized patients completed Part B.

In brief, Study ITSA demonstrated that the PK and postprandial glucose (PPG) differences between LY900014 and Humalog following SC administration (0.2 U/kg via injection or CSII bolus infusion) prior to a mixed-meal tolerance test (MMTT) are similar in pediatric patients with T1D as those observed in adults with T1D. In the context of the demonstrated safety and efficacy of LY900014 in the pediatric T1D population based on the data from Study ITSB, the similarity of PK/PD relationship between LY900014 and Humalog in pediatric and adult patients with T1D support the extrapolation of the safety and efficacy of CSII condition of use for LY900014, established previously from Study ITRO (pivotal CSII trial in adults with T1D, reviewed with BLA 761109/S-003) to the pediatric T1D population. To broaden the pediatric indication of LY900014 to include patients with T2D, the totality of data from the LY900014 clinical and PK/PD investigations in pediatric and adult patients with T1D and adults with T2D was considered. The analysis of the data from the individual studies included the use of models to characterize the PK of LY900014 and predict the efficacy in patients with pediatric T2D. The model-predicted insulin lispro PK profiles for patients with T2D showed that when LY900014 and Humalog were given prior to the start of meal or 20 minutes after the start of the meal, LY900014 had glucose lowering effect comparable to Humalog across all age groups of patients with T2D (children, adolescents and adults). These observations align with the PPG response observed in clinical pharmacology studies previously conducted in adults with T2D (Study ITRW, PK/PD study assessing mealtime and postmeal dosing in adults with T2D, reviewed with original submission of BLA 761109). Altogether, these data support the efficacy of LY900014 in pediatric patients with T2D.

The safety data collected from Study ITSB do not indicate a change to the safety profile of LY900014 previously established in adults with diabetes. No deaths occurred during the study and the incidence of serious adverse events (SAEs) was low and numerically higher for Humalog compared to LY900014 and LY+20 treatment groups. Three cases of diabetic ketoacidosis (DKA) occurred during the study, all in patients receiving LY900014; however, review of the case narratives revealed that 2 of the 3 cases resulted from missed insulin doses, thus no safety concern is raised based on this slight imbalance.

The hypoglycemia safety profile for LY900014 was found to be similar to Humalog. Severe hypoglycemia events were rare and balanced between treatment groups. No significant differences between treatment groups were noted for the incidences or rates of all documented hypoglycemia, nocturnal hypoglycemia, and non-nocturnal hypoglycemia for blood glucose (BG) < 54 mg/dL. When hypoglycemia was analyzed

relative to the time of the most recent dose, the differences in rates and incidences of hypoglycemia between treatment groups predictably correlated with the time action profile of the insulin and dosing, i.e., LY900014 group had greater hypoglycemia at timepoints ≤ 2 hours, LY+20 at timepoints >2 and ≤ 4 hours, and Humalog at timepoints > 4 hours.

The incidence of treatment emergent adverse events (TEAEs) was similar between Humalog and the pooled LY900014 treatment groups (All LY900014) with the exception of injection site reactions. Injection site AEs occurred in 6.2% of All LY900014 group compared to 2.7% of Humalog group; however, the severity was reported as mild (5.7%) or moderate (0.5%) in all cases and less than 0.5% of patients receiving LY900014 discontinued treatment due to AEs related to injection site reactions.

In summary, the safety data from Study ITSB in pediatric patients with T1D are comparable to those for LY900014 established from the pivotal adult T1D trial. From a safety perspective, the reassuring findings of LY900014 demonstrated in pediatric patients with T1D are also supportive for the use for LY900014 in the T2D population, because clinically, AEs with LY900014, such as hypoglycemia, would be more likely to occur with insulin dependent patients who are more insulin sensitive. In addition, the PK/PD models also predict that the risk of hypoglycemia for LY900014 and Humalog are generally comparable for age groups of patients with T2D.

Although the PK/PD data from Study ITSA support the CSII condition of use of LY900014, Study ITSA was not designed to establish the incidence of infusion site reactions in the pediatric population. Safety data from the adult CSII program for LY900014 show the occurrence of infusion site reactions to be higher than injection site reactions with MDI use; however, no infusion site reactions were reported as SAEs, the majority of cases were mild or moderate in severity, and fewer than 4% of cases necessitated therapeutic discontinuation. Taking the totality of this information into consideration, I believe the benefit-risk profile for LY900014 remains favorable for use in the pediatric population but recommend that the potential increased risk of infusion site reactions with CSII use in the pediatric population should be added to the Pediatric Use section of the prescribing information (PI) in order to apprise HCP and patients of this potential risk as they consider initiating treatment with LY900014.

In summary, the clinical data package submitted with this sBLA supports the efficacy of LY900014 in the broad pediatric diabetes population and the CSII condition of use. The availability of an insulin with a faster time-action profile offers prescribers and patients the benefit of another therapeutic option to help manage glycemia and mitigate future complications. The safety profile of LY900014 from Study ITSB appears comparable to what has been previously established, and prescribers and patients can be informed about the potential increased risk of infusion site reactions with CSII with the inclusion of this information into Section 8.4 (Pediatric Use) of the PI. Based on the totality of evidence, I believe that benefit-risk assessment for LY900014 is favorable for the pediatric population, and I recommend approval of LY900014 for the indication to improve glycemic control in adult and pediatric patients with diabetes mellitus.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetes mellitus is a serious chronic medical condition characterized by hyperglycemia and includes two main types: T1D and T2D. • T1D is caused by autoimmune destruction of the pancreatic beta cells, which leads to impaired insulin production and secretion, and impaired glucose metabolism. • T2D is characterized by hyperglycemia either due to insulin resistance or a deficiency of insulin and is often associated with other metabolic derangements such as dyslipidemia, hypertension, and obesity. • Diabetes mellitus affects nearly thirty million people in the United States, the majority (90-95%) of whom have T2D, according to the Centers for Disease Control (CDC)[1]. • Acute life-threatening complications of T1D include diabetic ketoacidosis due to insulin deficiency, while chronic complications of both T1D and T2D include cardiovascular disease, retinopathy, nephropathy, and neuropathy[2].	Both T1D and T2D are serious, life-threatening conditions that can lead to serious morbidity and mortality if left untreated.
Current Treatment Options	• The results of the Diabetes Control and Complications Trial (DCCT)[3-9] demonstrated that intensive insulin therapy resulted in improved glycemic control as measured by HbA1c, which was associated with improved clinical outcomes in patients with T1D. • Due to the depletion of insulin secreting pancreatic beta cells, patients with T1D require exogenous insulin for survival. • Treatment options for T2D include lifestyle modifications, usually followed by the addition of one or multiple different medications, which may also include insulin. There are currently multiple classes	Intensive insulin therapy is the standard of care for patients with T1D. Patients with T2D also frequently require the use of insulin to achieve glycemic targets. The availability of insulins with different pharmacokinetic (PK) and pharmacodynamic (PD) profiles allows more therapeutic choices for pediatric patients to use in individualizing a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of pharmacologic treatments for T2D, most with multiple members of each class, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, sodium-glucose linked transporter (SGLT)-2 inhibitors, and glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. • The results of the Kumamoto Study[14] showed that intensive insulin therapy resulting in better glycemic control (HbA1c < 7.1%) prevents the progression of microvascular complications in patients with T2D. • Rapid acting insulin analogs may be administered subcutaneously (SC) as part of a basal-bolus regimen with MDI, or as continuous subcutaneous insulin infusion (CSII) using an external insulin pump, which may help some patients achieve stricter glycemic control by allowing better individualization of dosing.	regimen to control glycemia and minimize risk of future complications. Having additional insulins for the CSII condition of use is of particular benefit in the pediatric diabetes population because CSII offers greater flexibility than multiple daily injections (MDI) therapy and allows dosing in smaller increments for safer titration of insulin.
Benefit	• Study ITSB demonstrated that mealtime LY900014 is noninferior to mealtime Humalog in change in HbA1c from baseline to week 26 in pediatric patients with T1D. The estimated treatment difference of mealtime LY900014 versus mealtime Humalog (95% CI) was -0.01 (-0.15, 0.14), establishing noninferiority with the upper bound of the 95% confidence interval (CI) lower than the prespecified noninferiority margin (NIM) of 0.4. Results of sensitivity analyses were similar to the primary analysis. • Results of postmeal dosing of LY900014 (LY+20) is also noninferior to mealtime Humalog in change in HbA1c from baseline to week 26. The estimated treatment difference of LY+20 versus mealtime Humalog	Substantial evidence of efficacy was provided in the submission to support the use of LY900014 for the indication to improve glycemic control in adult and pediatric patients with diabetes mellitus. The findings of Study ITSB demonstrated noninferiority of LY900014 to Humalog in change from baseline HbA1c after 26 weeks. The results of the primary analyses were

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(95% CI) was 0.00 (-0.18, 0.18). • Study ITSA demonstrated that the PK and glucodynamic (GD) differences noted between LY900014 and Humalog in adult patients with T1D was maintained in pediatric patients with T1D when LY900014 is administered by injection or by CSII. • The totality of data from the LY900014 clinical and PK/PD investigations in pediatric and adult patients with T1D and adults with T2D was used to characterize the PK of LY900014 and predict the efficacy in patients with pediatric T2D. • The model-predicted insulin lispro PK profiles for patients with T2D showed that when 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 across all age groups of patients with T2D (children, adolescents and adults). These observations align with the PPG response observed in clinical pharmacology studies previously conducted in adults with T2D (Study ITRW). • The results of Study ITSA, in conjunction with previous investigations demonstrating the efficacy and safety of LY900014 in adults with T2D and the similarity of PK/PD profiles of adults with T2D and T1D, support extrapolation of efficacy of LY900014 to the T2D pediatric population.	robust to sensitivity analyses using alternative missing data assumptions. In Study ITSA, the demonstration of similarity of the PK/PD relationship between LY900014 and Humalog in pediatric and adult patients with T1D following CSII bolus supports the extrapolation of the efficacy of CSII condition of use for LY900014 previously established in adults with T1D (Study ITRO) to the pediatric patients with T1D. The Applicant's model-predicted insulin lispro PK profiles for patients with T2D align with the PPG response observed in clinical pharmacology studies previously conducted in adults with T2D (Study ITRW, PK/PD study assessing mealtime and postmeal dosing in adults with T2D, reviewed with original submission of BLA 761109). Altogether, these data support the efficacy of LY900014 in pediatric patients with T2D.
Risk and Risk Management	• In Study ITSB, the overall incidence of SAEs, TEAEs, and clinically significant hypoglycemia was similar between LY900014 and Humalog. • No significant differences between treatment groups were noted for the incidences or rates of all documented hypoglycemia, nocturnal,	In general, the safety profile for LY900014 in the pediatric population appears to be similar to that in the adult population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and non-nocturnal hypoglycemia for blood glucose (BG) < 54 mg/dL. • When hypoglycemia was analyzed relative to the time of the most recent dose, the differences in rates and incidences of hypoglycemia between treatment groups predictably correlated with the time action profile of the insulin and dosing, i.e., LY900014 group had greater hypoglycemia at timepoints ≤ 2 hours, LY+20 at timepoints >2 and ≤ 4 hours, and Humalog at timepoints > 4 hours. • The of incidence the TEAEs of injection site reactions was significantly higher with LY900014 than with Humalog in ITSB. • In the adult studies, the incidence of infusion site reactions was greater than injection site reactions. • In the LY900014 clinical program, the vast majority of injection/infusion site reactions have been mild or moderate in severity and none have been SAEs, and discontinuations due to these AEs occur in less than 3% of patients receiving LY900014. • The incidence of infusion site reactions in the pediatric population is an uncertainty and may be higher than with multiple daily injection (MDI) therapy. • The overall benefit-risk assessment of LY900014 for the pediatric population remains favorable. • The label for LY900014 should include labeling that informs HCPs and patients of the potential increased risk of AEs of infusion site reactions.	The hypoglycemia safety profile for LY900014 was found to be similar to Humalog. Overall risk of hypoglycemia with LY900014 is similar to Humalog; however, the timing of hypoglycemia occurs earlier in the postdose periods with LY900014 and LY+20 than Humalog. The risk of infusion site reactions may potentially be higher than injection site reactions in the pediatric population; however, the benefit-risk remains favorable for LY900014 in the pediatric population. By ensuring adequate labeling, health care providers (HCP) and patients will be better informed when deciding whether LY900014 will be an appropriate therapeutic option.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Relevant patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. The 2020 National Diabetes Statistics Report from the Centers for Disease Control (CDC) estimates that 34.2 million Americans (10.5 % of the US population) are currently living with diabetes[1]. Both T1D and T2D are serious chronic disorders characterized by hyperglycemia.

Approximately 5% of the people with diabetes have T1D. This form of diabetes is usually diagnosed in children and young adults and is generally caused by autoimmune destruction of pancreatic β-cells, resulting in deficiency of insulin secretion. Patients with T1D are thus dependent upon insulin replacement for survival.

Approximately 95% of patients with diabetes have T2D. The etiology of T2D is multifactorial, but the underlying pathophysiology is believed to be insulin resistance and a relative insulin deficiency with inadequate insulin production to maintain euglycemia. Management of glucose control in T2D patients includes diet, weight control, and anti-diabetic drugs (both oral and injectable). Insulin may also be required for adequate glycemic control when other therapies are not tolerated or are ineffective in achieving glycemic targets.

Long-term hyperglycemia and metabolic changes over the course of T1D and T2D increase the risk for macrovascular (e.g., myocardial infarction, stroke) and microvascular (e.g., retinopathy, nephropathy) complications[2]. Results from the Diabetes Control and Complication Trial (DCCT)[3-9], United Kingdom Prospective Diabetes Study (UKPDS)[2, 10-13] and the Kumamoto Study[14] suggest that improved glycemic control (as measured by HbA1c) results in improved outcomes.

2.2. Analysis of Current Treatment Options

Marketed insulin products include short-acting insulin, rapid-acting insulin, intermediate-acting insulin, and long-acting insulin; however, insulin products labeled for CSII delivery are limited to rapid-acting insulin analogs and are limited to concentrations of 100 unit/mL. Rapid-acting insulins include insulin glulisine (Apidra), insulin lispro (Humalog, Admelog), and insulin aspart (NovoLog, Fiasp). Insulin lispro-aabc (Lyumjev) is currently only approved for CSII use in the adult population.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lyumjev was approved by FDA on June 15, 2020, and is indicated to improve glycemic control in adults with diabetes mellitus. Both concentrations of Lyumjev are labeled for SC administration at the start of a meal or within 20 minutes after starting a meal. Lyumjev 100 units/mL is also approved for the IV administration under medical supervision. On August 13, 2021, Lyumjev 100 units/mL received FDA approval for CSII condition of use in adults with diabetes and is labeled for use with the Insulet Omnipod Insulin Management System and Omnipod DASH Insulin Management System.

3.2. Summary of Presubmission/Submission Regulatory Activity

The clinical program for LY900014 was developed under the Investigational New Drug Application (IND) 127210. A summary of the clinical advice related to the pediatric development program relayed during key regulatory interactions between the Applicant and the Agency is provided below.

April 19, 2017: Type B Meeting- End of Phase 2 (EOP2) Meeting occurred. FDA agreed that the non-clinical data appeared to be adequate to support the safety of studying pediatric populations under IND, and a juvenile animal toxicity study would not be necessary to support investigations.

June 13, 2017: The applicant submitted an initial Pediatric Study Plan (iPSP).

September 8, 2017: FDA provided Written Response to the iPSP with the following information:

- FDA agreed that the Applicant's proposal for extrapolation and modeling to support the efficacy in pediatric patients with T2D appeared to be reasonable (i.e., use of data from clinical studies and PK/PD investigations in pediatric patients with T1D, adults with T1D, and adults with T2D in order to characterize the PK of LY900014, predict the efficacy, and recommend a dosing algorithm in youths with T2D).
- FDA agreed to the plan for partial waiver for the assessment of pediatric patients < 10 years of age with T2D.
- FDA did not agree with the Applicant's plan (b) (4) FDA recommended enrollment of children down to 1 year of age.
- FDA noted that the Applicant is not proposing to conduct a CSII clinical trial in the pediatric population, and advised that in order to be labeled for administration via CSII in the pediatric population, an assessment must be submitted to support this condition of use.

September 11, 2017: Applicant sent email correspondence acknowledging that a pediatric assessment will be needed for CSII condition of use in labeling.

October 13, 2017: Applicant submitted revised iPSP incorporating FDA recommendations.

November 1, 2017: FDA provided additional comment to the Applicant's iPSP requesting updates of estimated protocol submission dates.

November 9, 2017: Applicant submitted Agreed iPSP which included updated estimated submission dates for protocols.

November 15, 2017: Applicant submitted ITSA protocol.

December 4, 2017: FDA confirmed agreement with the Agreed iPSP, which included pediatric PK study (Study ITSA) and safety and efficacy study (Study ITSB).

February 9, 2018: Lilly requested Type C meeting to seek agreement on pediatric Study ITSB protocol and statistical analysis plan (SAP). FDA granted request as Written Responses Only (WRO). Applicant submitted background materials, draft protocol, and SAP March 9, 2018.

April 23, 2018: FDA provided WRO on the design of Study ITSB and the SAP.

- FDA advised that the proposed study duration of 26 weeks remains a review issue and that the need for a safety extension would be determined following review of the data from the adult studies.
- FDA did not agree with the Applicant's proposal (b) (4)
- FDA advised that if the Applicant wishes to pursue an indication allowing postmeal dosing in the pediatric population, then clinical trial data will be required to support this dosing (i.e., pediatric trial must include a postmeal dosing arm).

June 8, 2018: Applicant submitted updated protocol and SAP for Study ITSB to address FDA's comments from WRO. Applicant acknowledged the 26-week study duration remains a review issue, but maintained that 26 weeks is appropriate based on the existing data. The Applicant removed (b) (4) and included a postmeal Lyumjev dosing arm into Study ITSB.

June 19, 2018: FDA confirmed that the inclusion of the postmeal Lyumjev dosing arm in Study ITSB did not require an amendment to the iPSP (the increased patient numbers and enrollment

time did not impact the timelines in the Agreed iPSP).

July 23, 2018: FDA issued Advice/Information Request with additional feedback on the SAP for Study ITSB submitted on June 8, 2018.

December 9, 2019: Applicant submitted ITSB protocol amendment (a) in which it was proposed that in lieu of fingerstick blood glucose assessments, patients using personal CGM (b) (4) devices may use them for 4-point glucose testing during the study in trial locations where these devices are approved to guide insulin dosing decisions.

December 13, 2019: In response to ITSB protocol amendment (a), FDA sent an email correspondence to the Applicant to recommend the use of only FDA approved CGM systems for replacement of fingerstick blood glucose testing for treatment decisions (4-point glucose testing). FDA continued to recommend fingerstick glucose testing for 7-point glucose values and for confirmation of hypoglycemia.

December 17, 2019: In an email correspondence, the Applicant confirmed that patients could only use CGM device for daily 4-point SMBG to help investigator guide dosing decisions and reduce burden on patient (and only in countries/sites where use of these devices were approved for use in the pediatric population). These 4-point BG values would not be part of the study analyses. The Applicant stated that 7- point BGs would be collected by finger sticks using the study-provided BG meter. Confirmation of hypoglycemic symptoms would also be performed via finger sticks. FDA confirmed the Applicant's plans on December 18, 2019, and provided no further comments.

April 6, 2020: The Applicant submitted an email correspondence to notify FDA that for Study ITSB, screening was paused due to the global COVID-19 pandemic and the following mitigations were being implemented concerning the conduct of the trial:

- On-site visits can be converted to telephone visits at the site's discretion
- Visit windows for study visits can be extended as needed. The window cannot extend past a time period where there is investigational product (IP) interruption for more than 14 days.
- Several options for IP delivery can be implemented in the circumstance where a patient cannot attend an on-site visit. Each option ensures oversight of process and that IP is kept within storage conditions on the label.
    - Delivery of IP to the patient outside of the facility
    - Delivery of IP by site staff to the patient's home
    - Delivery of IP by a qualified vendor from site to the patient's home
- When on-site visits are not possible, lab data can be collected via local laboratory and the lab data will be entered by the site into the eCRF.

June 15, 2020: FDA approved BLA 761109 for the indication to improve glycemic control in

adults with diabetes mellitus and issued a Post Market Requirement (PMR 3874-1) to ensure completion of Study ITSB.

November 16, 2020: Applicant submitted ITSB SAP version 2.

December 21, 2020: FDA provided an email correspondence confirming that changes to version 2 of the SAP were acceptable and requested that Applicant respond to prior advice provided July 23, 2018, as not all comments had been addressed in SAP.

January 25, 2021: Applicant submitted a revised SAP (version 3) and provided response clarifying where revisions were made in the SAP in response to prior advice from July 23, 2018.

August 13, 2021: Supplement 003 for BLA 761109 to add CSII as a condition of use in adult patients was approved by FDA.

October 14, 2021: Supplement 004 for BLA 761109 for pediatric indication and CSII condition of use was filed.

3.3. Foreign Regulatory Actions and Marketing History

Lyumjev was first authorized on March 24, 2020, in the European Union (EU) for improvement of glycemic control in adults with diabetes mellitus. Lyumjev has since been authorized in 46 countries, including those in the EU, Japan, Switzerland, Brazil, and Korea. All countries have approved Lyumjev for SC, IV and CSII route of administration in adults with diabetes mellitus. At the time of this review, Lyumjev has not received approval for pediatric use in any foreign countries.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An Office of Scientific Investigations (OSI) audit was conducted, and details of the findings are provided in the Clinical Inspection Summary by Ling Yang, MD, PhD dated August 31, 2022. The audit involved clinical investigator site inspections for two domestic clinical sites involved in the Study ITSB. The sites selected had not previously been inspected and were flagged as having enrollment of large numbers of study subjects. Inspections of these sites found no significant regulatory violations. Based on the results of inspections and the regulatory assessments, OSI concluded that Study I8B-MC-ITSB appears to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the Applicant appear acceptable in

support of the indication.

4.2. Product Quality

The formulation of Lyumjev used in the clinical trials for this supplement is the same as the product used in the clinical development program supporting the BLA and is same as the marketed Lyumjev product.

4.3. Clinical Microbiology

Not applicable for this supplement.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable for this supplement.

4.5. Clinical Pharmacology

A summary of the key findings of Study ITSA and PK/PD modeling and simulations reports are briefly presented in this section. Additional details of Study ITSA and the population PK and PK/PD models are available in the review completed by the Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) dated September 24, 2022. The OCP/DCEP review team (Snehal Samant MS, PhD; Xiaolei Pan PhD; Justin Earp PhD; Jaya Vaidyanathan, PhD) has concluded that the data submitted are acceptable and support approval of BLA 761109/ S-004 to expand the indication for Lyumjev to pediatric patients with diabetes mellitus and to add CSII as a condition of use in the pediatric population.

The Applicant used the data from the clinical pharmacology studies used for registration of LY900014 in adult patients with T1D and T2D, as well as data from Study ITSA, to evaluate and estimate the PK/PD and efficacy of LY900014 in patients with T2D from 10 to <18 years of age. The summary of key clinical pharmacology and modeling findings has been excerpted from the OCP review.

Study ITSA design
Study ITSA was a phase 1, randomized, double-blind, 2-period crossover study designed to compare the PK and glucodynamic profiles (postprandial glucose excursion) of LY900014 and Humalog following SC administration of 0.2 U/kg in children (6 to <12 years), adolescents (12 to < 18 years) and adults (18 to <65 years) with T1D.

The study was comprised of 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 infusion via CSII.

All patients received the same individualized bolus insulin dose for both LY900014 and Humalog and the content of their mixed meal tolerance test (MMTT) was kept constant throughout the crossover periods.

Inclusion criteria:
Key inclusion criteria for this study were male or female subjects with a diagnosis of T1D between ≥6 and <65 years of age; 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 HbA1c ≤10% at screening.

Number of patients:
For Part A, 42 patients were randomized and 41 completed the study.
For Part B, 39 patients were randomized and 37 patients completed the study.

Key pharmacology and modeling findings
For patients with T1D when insulin lispro was 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 ($AUC_{[0\text{-}15min]}$) by 6.5-fold in children, by 3.5-fold in adolescents, and by 5.1-fold in adults with LY900014 compared to Humalog.
- The overall mean serum insulin lispro systemic exposure ($AUC_{[0\text{-}5h]}$), mean change from baseline [CFBL] $AUC_{[0\text{-}5h]}$, 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 T1D patients when LY900014 and Humalog 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 T1D.

For T2D patients via MDI:

- The model-predicted insulin lispro PK profiles in children and adolescents with T2D 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.

Key safety findings
LY900014 was well tolerated following a single SC bolus given as an injection or via CSII in pediatric and adult patients with T1D. No clinically meaningful differences were noted in the tolerability between pediatric and adult patients. There were no deaths or events of severe hypoglycemia. There were no discontinuations due to TEAEs. The sole SAE reported during the study was an unrelated SAE of abdominal trauma occurring 2 days after receiving the last dose of study drug. In summary, the findings of this PK/PD study revealed no new safety findings for the already established profile for LY900014.

Reviewer comment: *In brief, Study ITSA demonstrated that the PK and PPG differences between LY900014 and Humalog following SC administration (via injection or CSII bolus infusion) prior to MMTT are similar in pediatric patients with T1D and adults with T1D. In the context of the demonstrated safety and efficacy of LY90014 in pediatric patients with T1D based on the data from Study ITSB, these PK/PD data from Study ITSA support the extrapolation of the efficacy of CSII condition of use for LY900014 previously established in adults with T1D (Study ITRO, the pivotal CSII trial in adults with T1D, reviewed with BLA 761109/S-003) to the pediatric T1D population.*

To broaden the pediatric indication of LY900014 to include patients with T2D, the Applicant proposed that the totality of data from the LY900014 clinical and PK/PD investigations in pediatric patients with T1D, adults with T1D, and adults with T2D would be used to characterize the PK of LY900014 and predict the efficacy in patients with pediatric T2D (see discussion of iPSP in presubmission history in Section 3.2). The model-predicted insulin lispro PK profiles for patients with T2D showed an accelerated absorption and a reduction in the late insulin exposure with LY900014 compared to Humalog across all age groups of patients (i.e., children, adolescents, and adults). In addition, model-based PK/PD simulations showed that when both insulins were given prior to the start of meal or 20 minutes after the start of the meal, LY900014 had a comparable glucose lowering effect than Humalog in all age groups of patients with T2D. These observations align with the PPG response observed in clinical pharmacology studies previously conducted in adults with T2D (Study ITRW, PK/PD study assessing mealtime and postmeal dosing in adults with T2D, reviewed with original submission of BLA 761109). The clinical pharmacology team concluded that the evidence from PK/PD modeling and simulations support the use of LY900014 in pediatric patients with T2D.

From a safety perspective, I believe that the reassuring safety profile of LY900014 demonstrated in studies of pediatric patients with T1D supports a favorable benefit-risk profile for LY900014 use in the T2D population, because AEs with LY900014, such as hypoglycemia, would be more likely captured with insulin dependent patients who are more insulin sensitive. In addition, the models also predict that the risk of hypoglycemia for LY900014 and Humalog are generally comparable for age groups of patients with T2D.

4.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) was consulted to review the available data submitted by the Applicant and opine on the safety and appropriateness of the CSII condition of use for Lyumjev in the pediatric population, based upon the Applicant's proposed extrapolation strategy. L. Catherine Tello, MD reviewed the submission for the Division of Chemistry and Toxicology Devices from the Office of In Vitro Diagnostics and Radiological Health (OHT7). For details of her review, see the Inter-Center Consult (ICCR# 000814433) dated September 7, 2022. Based on the review of the key issues summarized below, CDRH supports approval of Lyumjev for the CSII condition of use in the pediatric population.

To support the CSII condition of use in the pediatric population, the Applicant submitted the efficacy and safety data from the pivotal pediatric trial, Study ITSB, in patients with T1D as well as the PK/PD information from Study ITSA. The data from Study ITSA, and the Applicant's modeling, demonstrate that the PK and PPG differences between LY900014 and Humalog observed in adults with T1D are maintained in pediatric patients with T1D, and this similarity is noted whether Humalog and LY900014 are administered as SC injections or as SC infusions via CSII. Based on these PK/PD data, the efficacy demonstrated from the pivotal CSII trials in adults with T1D (i.e., Study ITRO, reviewed with submission of BLA 761109/S-003) can be extrapolated to pediatric patients using CSII.

In order to assess the potential risk of device-related safety issues (e.g., infusion site reactions, unplanned infusion set changes, occlusions) of Lyumjev via CSII in the pediatric population, Dr. Tello reviewed the information from previous CDRH consults for the clinical program for LY900014 and submitted and information request (IR) to the Applicant, asking for data from publications, postmarket data, or other use of LY900014 in pediatric patients outside the U.S. to support pediatric pump use. Additionally, she requested safety subgroup analyses of the data from the subset of patients from Study ITRO with the lowest total daily insulin (TDI) needs as these doses would be most comparable to those used by the pediatric population.

Because LY900014 is not approved for pediatric use in any country, there were no publications pertaining specifically to LY900014, and patient experience was limited to off label use in pediatric patients. In general, the diabetes literature cites that injection and infusion site reactions are commonly reported in children, but they rarely result in serious clinical outcomes.

The initial analyses of Study ITRO data suggested a higher rate of pump occlusion alarms for the subgroup of patients receiving mid-range doses of 20 to 40 U/day in comparison to the lowest subgroup of < 20 U/day or the total trial population. This finding prompted an additional IR to the Applicant in order to examine the relationship between TDI in greater detail by smaller subgroups of TDI (i.e., < 20 U/day, 20-30 U/day, 30-40 U/day and > 40 U/day). With this analysis, the 20-30 U/day subgroup continued to have a higher rate of occlusion alarms than the other subgroups; however, a dose-response relationship for pump occlusion alarms with LY900014 was not evident. In addition, the lowest dose subgroup of < 20 U/day had no cases of occlusion alarms. Further, all of the subjects of the subgroup in question with occlusion alarms had mild to moderate AEs without any serious clinical sequelae such as diabetic ketoacidosis (DKA), suggesting that the alarms were serving their purpose by alerting patients to preemptively take action and correct any issues with their infusion sets. Finally, the data in the 20-30 U/day subgroup appeared to be skewed by a single patient reporting 11 unplanned infusion set changes compared to other participants experiencing only 1.

Taking the totality of this information into consideration, Dr. Tello concluded that there do not appear to be higher device-related risks with LY900014 than Humalog via CSII for adults with lower TDI doses most representative of those of potential pediatric users; therefore, these data support the general safety of clinical use of LY900014 via CSII in the pediatric population. She also did not believe that additional questions of safety related to pump programming parameters need to be addressed, given that the labeling for Lyumjev already recommends individualization of pump parameters with the CSII condition of use. As discussed in greater detail in the review of safety, particularly in Section 8.5.2, and in the discussion of labeling in Section 10.1, Dr. Tello agreed that the Lyumjev label should be revised to adequately inform prescribers of the higher incidence of injection site reactions in the pediatric T1D trial compared to the adult trials, and the potential for higher risk of infusion site reactions in the pediatric population with CSII use.

4.7. Consumer Study Reviews

Not applicable to this submission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1. Efficacy and Safety Studies Relevant to Submission

Trial Identity	Trial Design Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety						
18C-MC-ITSB (PRONTO-Peds) NCT03740919 Initiation date: April 7, 2019 Completion date: July 2, 2021	*Trial Design*: Phase 3, prospective, randomized, treat-to-target, multinational, 3-treatment group, parallel, active-controlled study in pediatric patients with T1D on MDI regimen. *2 Double-Blind Treatment Groups*: *Mealtime*: LY900014 or Humalog dosed SC 0-2 minutes prior to start of each meal. *Open Label Treatment Group*: *Postmeal*: LY+20 dosed SC 20 minutes after the start of a meal Basal Insulin During Study: • glargine U-100 qd or bid • detemir U-100 qd or bid • degludec U-100 qd	*Primary endpoint:* HbA1c at 26 weeks change in baseline *Primary Objective:* To demonstrate that LY900014 is noninferior to Humalog on glycemic control (NIM = 0.4% for HbA1c) in pediatric patients with T1D, when administered as prandial insulin (0 to 2 minutes prior to meal), in combination with basal insulin. *Multiplicity adjusted objectives:* To demonstrate that LY900014+20 is noninferior on glycemic control (NIM = 0.4% for HbA1c) compared to Humalog administered as prandial insulin. Demonstrate that LY900014 is superior to Humalog on glycemic (HbA1c) control when administered as prandial insulin (0 to 2 minutes prior to the meal)	*26-week treatment period* (open-label treatment) with 26-week primary endpoint 1-week screening 4-week lead-in 26-week treatment period 2- week safety follow-up	*Randomized/* *Safety Population*: 716 randomized: Humalog: 298 LY900014: 280 LY+20: 138	Diagnosis of T1D for at least 6 months age 1 to <18 years weight ≥ 16 lbs MDI ≥ 90 days using only 1 of the following rapid acting insulin analogs: • lispro U-100 • aspart U-100 • glulisine U-100 • fast acting aspart HbA1c ≤9.9%	*96 centers in 17 countries*: U.S. Russian Federation, Czech Republic, Spain, Ukraine, Brazil, Israel, France, Italy, Poland, United Kingdom, Mexico, China, Austria, Germany, Denmark, and Japan.
Clinical Pharmacology Study						
I8B-MC-ITSA Initiation date: March 27, 2018 Completion date: November 14, 2019	*Trial Design*: Multicenter, Phase 1, randomized, 2-part, patient- and investigator-blind, 2-period, crossover study in children, adolescents, and adults with T1D currently using a CSII pump or an MDI regimen *Part A*: Patients received a single	*Primary objective:* *Part A*: -To evaluate the PK of insulin lispro following a single dose (0.2U/kg administered as SC injection) of LY900014 compared to Humalog in children, adolescents, and adults with T1D. *Part B*:	*Screening period*: 28 days *Treatment period*: 2 inpatient days across 2 study periods separated by 22 days *Follow-up*: ≥ 14 days after last dose	*Randomized*: *Part A*: Randomized: 42 Treated (at least 1 dose): 42 Completed: 41 *Part B*: Randomized: 39	Patients with T1D *Age:* Children: 6 to <12 years Adolescents: 12 to <18 years	*3 study centers in 3 countries*: U.S. Canada Germany

	dose of LY900014 and Humalog on 1 occasion each as SC bolus via injection *Part B*: Patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus via CSII	-To evaluate the PK of insulin lispro following a single dose (0.2 U/kg administered as SC infusion via Medtronic 640G or 630G) of LY900014 compared to Humalog in children, adolescents, and adults with T1D. *Secondary objectives (A & B)*: -To evaluate the GD response to LY900014 and Humalog administered through SC bolus injection or CSII, as assessed using the MMTT in children, adolescents, and adults with T1DM. -To evaluate the tolerability of LY900014 following SC injection or CSII in children, adolescents, and adults with T1D.		Treated (at least 1 dose): 37 Completed: 37	Adults: 18 to <65 years	
CSII = continuous subcutaneous insulin infusion; GD = glucodynamic; MDI = multiple-daily-injection; MMTT = mixed meal tolerance test; NIM = noninferiority margin; PK = pharmacokinetics; SC = subcutaneous; T1D = type 1 diabetes.						

5.2. Review Strategy

The focus of this clinical review is Study ITSB, a randomized, double-blind, active-controlled clinical trial providing data to support the efficacy and safety for the use of LY900014 to improve glycemic control in the pediatric T1D population. The key findings of Study ITSA, which provides data to allow extrapolation of use of LY900014 to pediatric patients with T2D and to support the CSII condition of use, are discussed in Section 4.5.

The analyses used to formulate my conclusions of efficacy and to determine the information included in labeling are those which were conducted and/or corroborated by the FDA statistical reviewer, Wenda Tu, PhD. Key tables summarizing the analyses of the primary and multiplicity adjusted endpoints are presented in Section 6.1.2. Refer to the Office of Biostatistics DBII Review for more detailed discussion of efficacy analyses by Dr. Tu dated August 16, 2022.

Clinically relevant supportive secondary endpoints, such as proportion of subjects reaching HbA1c targets and changes in insulin dose, are included in the efficacy section, while endpoints assessing immunogenicity and hypoglycemia are discussed under submission specific safety issues in Section Error! Reference source not found.. Select exploratory secondary endpoints are briefly discussed. Refer to Section 8.1 for safety review approach.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study ITSB

Study title: A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes: PRONTO-Peds

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to demonstrate that LY900014 is noninferior to Humalog on glycemic control as measured by change from baseline to Week 26 in HbA1c (non-inferiority margin [NIM] = 0.4%) when administered as mealtime insulin (0 to 2 minutes prior to meal) in combination with basal insulin (insulin glargine, insulin degludec, or insulin detemir) in pediatric patients with T1D.

Multiplicity-adjusted objectives were to demonstrate that LY900014 is:

- noninferior to Humalog on glycemic control as measured by change from baseline to Week

26 in HbA1c (NIM= 0.4%) when LY900014 is administered 20 minutes after the start of a meal and Humalog is administered as mealtime insulin

- superior to Humalog on glycemic control as measured by change from baseline to Week 26 in HbA1c when administered as mealtime insulin.

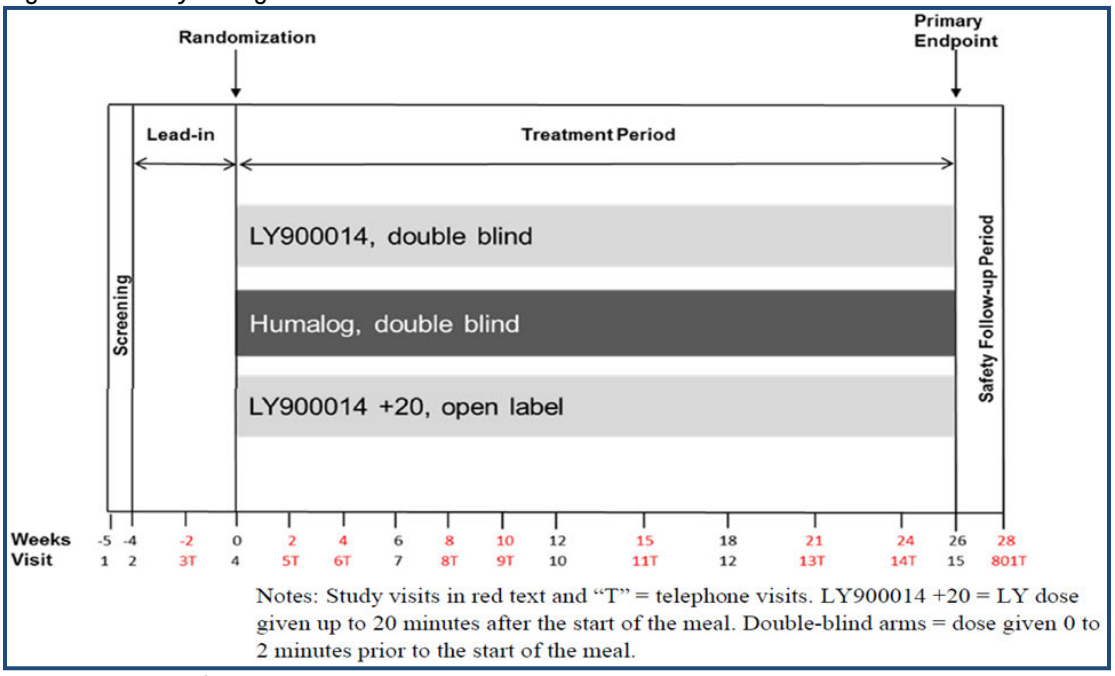
Trial Design (see Figure 1 for Study Design and Table 21 for Study Schedule of Assessments)

Study ITSB was a phase 3, prospective, randomized, outpatient, multinational, multicenter, parallel, active-controlled study conducted in children and adolescent patients with T1D 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.

In 2 of the treatment groups, LY900014 or Humalog was administered immediately (0 to 2 minutes) prior to each meal in a double-blind manner. A third open-label treatment group consisted of LY900014 administered minutes after the start of a meal (LY+20).

Reviewer comment: The trial design for ITSB and study endpoints were discussed and agreed upon with the Division before study initiation. Per the Division's advice, the Applicant included a an open-label postmeal dosing arm to the protocol in order to provide data to support the postmeal dosing in the pediatric population.

Figure 1. Study Design ITSB



Source: CSR ITSB Figure ITSB.3.1.

After screening, eligible patients entered a 4-week lead-in period during which they were switched from their pre-study prandial insulin to marketed insulin lispro (Humalog) while continuing their basal insulin regimen (insulin glargine, insulin detemir, or insulin degludec) throughout the study.

At the end of the lead-in period, a total of 716 patients were randomized to their investigational product (IP) in a 2:2:1 ratio as follows: double-blind mealtime LY900014, double-blind mealtime Humalog, or open-label LY+20. Stratification factors included the following: country; HbA1c at screening (≤8.0% vs >8.0%); type of basal insulin (insulin glargine, detemir, or degludec); and age group (1 to <12 years vs 12 to <18 years). Assignment to treatment groups was determined by a computer-generated random sequence.

The IPs used in this trial were in provided in disposable, prefilled insulin pens which allowed for dosing in half-unit increments and could dose between 0.5 and 30 units per injection. FDA approved blood glucose (BG) meters were also provided to study participants. The BG meter was used to perform all 7-point glucose tests and for glucose confirmation during hypoglycemia events.

Patients were permitted to determine their IP dose by pattern adjustment or carbohydrate counting, but were required to maintain the same dosing method throughout the study.

- Pattern adjustment: The patient is prescribed a fixed dose or dose range of insulin for each meal. The fixed insulin dose may be individualized for each meal.
- Carbohydrate counting: The patient performs carbohydrate counting for prandial insulin dosing; prandial insulin dose is based upon the estimated carbohydrate content of the meal (as unit of insulin per grams carbohydrate).

Insulin doses were actively titrated during the lead-in period and the first 12 weeks of the treatment period. Glucose target values (Table 2) were used to determine the insulin dose titration. Patients were required to collect glucose values at least 4 times (before meals and bedtime) each day, which were reviewed by the investigator to guide titration of basal and prandial insulin doses. During the lead-in, emphasis was placed on basal insulin dose adjustment. Prandial insulin was not adjusted during the lead-in period unless required for patient safety.

During the first 12 weeks of the 26-week treatment period, prandial insulin dosing was actively optimized. The prescribed insulin doses were determined by, and was the responsibility of, the investigator in consultation with the patient or caregiver. In addition to adjusting insulin dosing to achieve the target glucose values, modifications in the calculation of the insulin dose may have been influenced by other clinical circumstances and safety considerations known to the investigator. Although most of the insulin titration occurred during the lead-in and first 12

weeks of treatment period, adjustments of basal and prandial insulin doses were permitted to continue throughout the treatment period in order to achieve or maintain glycemic targets based on changes in lifestyle, individual circumstances or for safety reasons. The primary endpoint HbA1c at Week 26, therefore, reflected glucose control during the 3-month time period when there were the fewest changes in therapy.

After completion of the study treatment, or early discontinuation (ED), patients returned to their pre-study prandial insulin treatment.

Table 2. Glucose Target Values[1]

	Target Range
Before meals	70 - 130 mg/dL
Postprandial (1 hour)	90 to 180 mg/dL
Bedtime	80-140 mg/dL
HbA1c	<7.0%

Abbreviations: HbA1c = hemoglobin A1c; w/out = without
Source: Clinical Protocol ITSB (b) Table ITSB.4.

Procedures and study schedule (See also Table 21 for Schedule of Assessments):
The following activities occurred at the listed time points.

-Review of concomitant medications, AEs, basal and prandial insulin dose assessments, hypoglycemia data, skin/injection site assessments:
- All visits

-HbA1c assessment:
- Screening, Week 0, 6, 12, 26, or early discontinuation (ED) visit

-Body weight, vital signs assessment:
- Screening, weeks -4, 0, 6, 12, 18, 26, ED

-Height assessment:
- Screening, weeks 0, 12, 26, ED

-Pregnancy testing:
- Screening, Week 0

-Hematology, chemistry assessment:

[1] International Society for Pediatric and Adolescent Diabetes (DiMeglio et al., 2018).

- Screening, Week 0, 26, ED

-Nutritional counseling, diabetes counseling:

- Week -4

-Titration of basal insulin:

- Week -4, -2, 0, 2, 4, 6, 8, 10, 12

-Titration of prandial insulin:

- Week 0, 2, 4, 6, 8, 10, 12

-Anti-insulin lispro antibody assessment:

- Screening, Week 0, 6, 12, 26, ED

Reviewer comment: *The trial design, duration, schedule of assessments, and choice of comparator appear to be appropriate. As it is not possible to compare LY900014 with placebo in subjects with T1D who are dependent upon insulin, Humalog, an insulin lispro product without the* (b) (4) *excipients of LY900014, was selected as the active comparator. The selection of insulin lispro as a comparator allows for comparison of efficacy, and also the effects of the excipients on the safety findings.*

The 4-week lead-in period provides sufficient time for wash-out of previously prescribed prandial insulin products and the 2-week safety follow-up period is also appropriate, given the short half-life of prandial insulin products. Basal insulin titration begins during the lead-in period and the study includes a 12-week titration period for the IP, followed by a relatively stable period of 12 weeks before assessment of HbA1c. Ideally, all treatment arms should achieve relatively stable glycemia and insulin dosing for 12 weeks before HbA1c assessment.

The investigator was permitted flexibility in continuing to adjust both basal insulin and IP throughout the treatment period, which makes it difficult to assess adherence to the titration algorithm; however, this flexibility is necessary to mitigate risk of DKA and hypoglycemia in this vulnerable population. The randomized, double-blind design with stratification by baseline HbA1c (<8% vs > 8%) helps to mitigate imbalances between study arms of patients who may require additional insulin adjustments throughout the study. It is notable the type of prandial insulin dosing (pattern vs carbohydrate counting) was not listed as a stratification factor. Patients dosing with carbohydrate counting have greater flexibility with dietary intake and therefore, in theory, could have greater variability in insulin doses on a day-to-day basis, which could result in differences in the incidence of hypoglycemia and/or differences in total daily insulin doses compared to patients with pattern dosing. However, based on the baseline patient characteristics presented in Table 4 , it appears that the treatment arms were balanced for the types of prandial dosing and therefore the results of safety and efficacy analyses should not be confounded by this covariate.

Key inclusion criteria:

- male and female 1 to < 18 years of age with T1D for at least 6 months at screening

- weight ≥ 16 pounds
- on MDI therapy for at least 90 days with only one of the following prandial U-100 insulins: lispro, aspart, glulisine, or fast-acting aspart
- on treatment with only one of the following basal U-100 insulin for at least 90 days: glargine QD or BID; detemir QD or BID; degludec QD
- total daily insulin dose of 0.3 to ≤ 1.9 U/kg
- female patients of childbearing potential not pregnant, not breastfeeding, and sexually abstinent or using highly effective method of contraception
- HbA1c ≤9.9%
- Informed assent and consent, as required per local guidelines

Key exclusion criteria:

- hypoglycemia unawareness
- >1 episode of severe hypoglycemia within 6 months of screening
- >1 emergency room visit or hospitalization due to hyperglycemia or diabetic ketoacidosis (DKA) within 6 months of screening
- use of CSII regimen for ≥ 14 days within 90 days of screening
- been on a treatment regimen that included regular human insulin, neutral protamine Hagedorn (NPH), Afrezza® (insulin human) inhalation powder, any premixed insulins, or use of diluted insulins within the last 90 days
- oral or injectable medication intended for the treatment of diabetes mellitus other than insulins within the last 90 days
- continuous subcutaneous insulin infusion regimen for ≥14 days within the 90 days
- other clinically significant disorder or uncontrolled concomitant disease that, in the investigator's opinion, would preclude participation in the trial or pose a safety risk
- history of blood transfusion or severe blood loss within 90 days prior to screening
- hemoglobinopathy, anemia, or other traits known to interfere with measurement of HbA1c

Reviewer comment: In general, the inclusion and exclusion criteria appear appropriate. Risk to patients was appropriately minimized by the exclusion of participants with hypoglycemia unawareness and/or a history of clinically significant hyperglycemia and/or DKA within 6 months. The HbA1c criterion was broadened to permit inclusion of a greater number of participants; however, assessment of treatment effect is more challenging in patients with values in the lower HbA1c range.

Study Endpoints

Primary endpoint:
Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c (baseline is defined as the last non-missing measurement at or before the randomization visit).

Multiplicity adjusted endpoints:

- Difference between LY+20 and Humalog in change in HbA1c from baseline to Week-26.
- Difference between LY900014 and Humalog in change in HbA1c from baseline to Week-26.

Other secondary endpoints:

- Rate and incidence of documented postdose hypoglycemic events within 1 and 2 hours after the prandial dose from Weeks 0 through 26.
- Rate and incidence of documented hypoglycemic events from Weeks 0 through 26.
- Rate of severe hypoglycemic events from Weeks 0 through 26.
- Change from baseline in total, basal, and prandial insulin doses and prandial/total insulin dose ratios at Week 26.
- Proportion of patient with HbA1c <7% and <7.5% at Week 26.
- Change from baseline to Week 26 in 7-point SMBG values.
- Change in weight (kg) from baseline to Week 26.
- Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 7-point SMBG profiles.
- Incidence of treatment-emergent anti-insulin lispro antibodies

Reviewer comment: The primary endpoint of change in HbA1c at Week 26 and NIM of 0.4% were agreed upon by the Division prior to study initiation. Hemoglobin A1c is a well-validated surrogate marker for the long-term microvascular complications of diabetes mellitus; thus, HbA1c is an acceptable clinical surrogate endpoint. The International Council for Harmonization (ICH) E10 states that the NIM cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of a planned trial. For diabetes studies, an NIM of 0.4% has historically been accepted as per the 2008 draft guidance, "Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention," which was still in place at the time of study design development.

Statistical Considerations

Sample size:

Sample size for the study was based on the NIM of 0.4% and randomization ratio of 2:2:1 for LY900014, Humalog, and LY+20, respectively. Assuming an NIM of 0.4%, no true difference between treatment arms, and an SD of 1.1%, approximately 240 completers in each double-blind treatment group provided at least 95% power to show noninferiority between LY900014 and Humalog in change from baseline to 26 weeks in HbA1c, using the upper limit of a 2-sided 95% confidence interval (LY900014 – Humalog). With 240 completers required for the Humalog arm, assuming an NI margin of 0.4%, a treatment difference of < 0.07%, 240 completers from Humalog arm and 120 completers from the LY+20 arm provide approximately 76% power to show NI of LY900014 postmeal to Humalog at mealtime. Assuming a 15% dropout rate for 26

weeks, approximately 708 subjects (LY900014 = 283; Humalog = 283; LY+20 = 142) were planned for the study.

Efficacy estimand:
The efficacy analysis was conducted on the randomized population. The treatment group was defined on the basis of the treatment the patients were assigned. The intention-to-treat (ITT) estimand, which includes all data regardless of intercurrent events, was analyzed by Dr. Tu for efficacy analyses used for regulatory purposes. The ITT population is defined as all randomized subjects, regardless of post-baseline result availability.

Handling of missing data:
The return-to-baseline approach was employed to handle missing data. Specifically, the patient-level baseline value plus a noise was used to impute missing endpoints. The noise follows a normal distribution with variability estimated from the "washout HbA1c data". The "washout HbA1c data" were derived by subtracting the mean treatment effect (calculated within each treatment arm) from individual non-missing HbA1c values at Week 26. The Applicant's return-to-baseline method differs from the Division recommended method, in which variability of the imputed endpoints is usually estimated from the primary analysis of covariance (ANCOVA) model based on completers' data. Thus, Dr. Tu performed the primary analysis based on the Division's preferred method; however, the results of both methods are noted to be identical up to two decimal places.

Efficacy analysis:
The primary efficacy analysis was performed based on an ANCOVA, with the change from baseline in HbA1c at Week 26 as the response variable, and treatment, baseline HbA1c and stratification variables (country, type of basal insulin, and age group) as covariates. The ANCOVA was performed on 1000 imputed datasets and the analysis results were integrated using Rubin's Rule. LY900014 was to be declared noninferior to Humalog if the upper limit of the 2-sided 95% confidence interval (CI) for the least squared (LS) mean difference in the change from baseline in HbA1c for LY900014 minus Humalog was below +0.4%. The superiority of LY900014 in controlling HbA1c compared to Humalog was also assessed. If the p-value was less than 0.05 or equivalently the upper limit of the CI is less than zero, LY900014 would be declared superior to Humalog.

Multiplicity adjustment:
A hierarchal testing procedure was used for multiplicity control of the hypothesis testing for the primary and key secondary objectives. Each test of treatment effect was conducted at a two-sided alpha level of 0.05, with the hierarchy specified below:

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

Sensitivity analysis:
Sensitivity analysis was performed using a one-way tipping point analysis. A penalty (delta) was added to the imputed values of the experimental arm and the same ANCOVA as applied to the primary analysis was performed on the delta-adjusted dataset to see whether the conclusion of the primary analysis was overturned. If not, the delta penalty was incremented, and the process was repeated until the primary result was overturned. The primary result would be robust to missing data if the delta required to overturn the primary result was not a plausible scenario in a real-word setting. Imputation under the NI null method was included as a special case of this tipping point analysis. Additionally, Dr. Tu performed a two-way tipping point analysis by tipping both the experimental arm and the control arm, following a similar procedure as described above.

Protocol Amendments

Protocol 18B-MC-ITSB was amended twice: Amendment (a) on November 18, 2019 (see details in review of pre-submission history in Section 3.2), and Amendment (b) on April 30, 2020, implemented due to the COVID-19 pandemic. This amendment allowed one re-screen for patients who had a screen fail or unexpectedly had to discontinue due to COVID-19 enrollment pause. Such patients would restart at Visit 1. In addition, changes were made in the inclusion criteria for total daily insulin dose range (0.5 to ≤ 1.5 U/kg changed to 0.3 to ≤ 1.9 U/kg) and HbA1c (value between ≥6.5% and ≤ 9.5% changed to value ≤ 9.9%). This amendment enabled a broader range of patients to participate (i.e., younger and active children, who require smaller doses; and adolescents, who require higher doses during puberty; and patients in good glycemic control).

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that studies ITSB and ITSA were conducted in compliance with the International Council for Harmonization 1996 Guideline for Good Clinical Practice as well as all applicable laws and regulations.

Financial Disclosure

In accordance with 21 CFR 54.4, the Applicant submitted Form 3454 for Study ITSB. The Applicant provided list of investigators, none had financial interests to disclose. See also Section 13.2 Financial Disclosure for additional details.

Patient Disposition

A total of 840 patients were screened and 716 patients were randomized. All randomized

subjects received at least one dose of the study drug. A summary of patient disposition for Study ITSB is presented in Table 3. No notable differences are observed across the treatment arms. The study and treatment discontinuation rates were low, with greater than 96% of patients completing the study and treatment. The most common reason for discontinuation of study and/or study treatment was *withdrawal by subject*.

Table 3. Patient Disposition, All Randomized Patients

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

* Information on "Missed Primary Endpoints" was provided by the reviewer based on the datasets: adsl and ada1c.
Source: Excerpted from FDA Statistical Review Table 3

Protocol Violations/Deviations

Important protocol deviations are defined as those likely to have a significant impact on the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. A total of 78 participants (10.9%) had at least 1 important protocol deviation and comprised generally similar proportions of each treatment arm: Humalog = 10.4%; LY900014 = 12.1%; LY+20 = 9.4%.

Demographic Characteristics Other Baseline Characteristics (Table 4)

A total of 716 patients were randomized into ITSB. Demographic and baseline clinical characteristics were generally consistent across the treatment groups. The mean age of patients was 12.3 years, with approximately 65% of participants 12 <18 years of age and less than 4% under 6 years of age. More than half of the patients were male (51.3%) and the majority of patients were White (89.1%), followed by Asian (5.6%), American Indian/Alaskan

Native (1.7%) and Black/African American (1.5%). In this multinational trial, Europeans comprised the majority (56.2%) of study participants, followed by the U.S. (17.7%).

The baseline disease characteristics for the diabetic participants revealed the mean duration of diabetes was 4.6 years and mean HbA1c at baseline was 7.8%. The mean body mass index (BMI) was 20.4 kg/m^2. The majority (54.7%) of participants received insulin glargine as basal insulin, followed by insulin degludec (36.2%), and insulin detemir (9.1%). The majority (79.5%) of patients used carbohydrate counting to determine prandial insulin doses over pattern adjustment (20.5%).

Table 4. Patient Demographics and Baseline Disease Characteristics

Demographic and Baseline Disease Parameters	Treatment Groups			
	Humalog (N = 298)	LY900014 (N = 280)	LY900014 + 20 (N = 138)	Total (N = 716)
Age				
Mean (SD)	12.39 (3.18)	12.10 (3.42)	12.32 (3.75)	12.26 (3.39)
Minimum, Maximum	3, 17	3, 17	4, 17	3, 17
1 to < 6 years, n (%)	7 (2.3)	10 (3.6)	10 (7.2)	27 (3.8)
6 to <12 years, n (%)	98 (32.9)	88 (31.4)	40 (29.0)	226 (31.6)
12 to < 18 years, n (%)	193 (64.8)	182 (65.0)	88 (63.8)	463 (64.7)
Sex, n (%)				
Female	140 (47.0)	144 (51.4)	65 (47.1)	349 (48.7)
Male	158 (53.0)	136 (48.6)	73 (52.9)	367 (51.3)
Ethnicity, n (%)*				
Hispanic or Latino	12 (24.0)	12 (22.6)	6 (25.0)	30 (23.6)
No Hispanic or Latino	38 (76.0)	41 (77.4)	18 (75.0)	97 (76.4)
Race, n (%)				
American Indian or Alaska Native	6 (2.0)	6 (2.1)	0	12 (1.7)
Asian	20 (6.7)	13 (4.6)	7 (5.1)	40 (5.6)
Black or African American	7 (2.3)	3 (1.1)	1 (0.7)	11 (1.5)
Multiple	4 (1.3)	0	1 (0.7)	5 (0.7)
Native Hawaiian/ Other Pacific Islander	2 (0.7)	0	0	2 (0.3)
Not Reported	3 (1.0)	2 (0.7)	3 (2.2)	8 (1.1)
White	256 (85.9)	256 (91.4)	126 (91.3)	638 (89.1)
Region, n (%)				
Asia	33 (11.1)	25 (8.9)	11 (8.0)	69 (9.6)
Europe	167 (56.0)	158 (56.4)	78 (56.5)	403 (56.2)
South America	48 (16.1)	44 (15.7)	25 (18.1)	117 (16.3)
United States	50 (16.8)	53 (18.9)	24 (17.4)	127 (17.7)
BMI (kg/m^2)				
Mean (SD)	20.3 (4.19)	20.5 (4.60)	20.5 (4.39)	20.4 (4.39)
Minimum, Maximum	12.8, 38.8	11.5, 38.0	14.1, 37.3	11.5, 38.8
Duration of Diabetes (years)				
Mean (SD)	4.7 (3.28)	4.5 (3.58)	4.6 (3.32)	4.6 (3.41)
Minimum, Maximum	0.5, 15.9	0.5, 16.5	0.5, 15.3	0.5, 16.5
Baseline HbA1c				
Mean (SD)	7.81 (0.91)	7.81 (0.87)	7.77 (0.85)	7.80 (0.88)
≤ 8.0%, n (%)	187 (62.8)	174 (62.1)	86 (62.3)	447 (62.4)
>8.0%, n (%)	111 (37.2)	106 (37.9)	52 (37.7)	269 (37.6)
Bolus Insulin Dosing Plan, n (%)				

Carbohydrate Counting	234 (78.5)	219 (78.2)	116 (84.1)	569 (79.5)
Pattern Adjustment	64 (21.5)	61 (21.8)	22 (15.9)	147 (20.5)
Lead-in Basal Insulin, n (%)				
Insulin degludec	108 (36.2)	105 (37.5)	46 (33.3)	259 (36.2)
Insulin detemir	26 (8.7)	23 (8.2)	16 (11.6)	65 (9.1)
Insulin glargine	164 (55.0)	152 (54.3)	76 (55.1)	392 (54.7)
Personal CGM Use, n (%)				
Yes	128 (43.0)	119 (42.5)	61 (44.2)	308 (43.0)

Abbreviations: BMI = body mass index; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c; N = number of subjects in population; n = number of subjects; SD = standard deviation.

* Only includes responses from U.S. sites.

Source: Excerpted and modified from FDA Statistical Review Table 4

Reviewer comment: The proportion of patients discontinuing the study or having important protocol deviations was similar between treatment arms and therefore should not significantly impact the interpretation of the safety and efficacy analyses. Treatment arms were generally balanced in terms of age, gender, BMI, and duration of T1D. Numerically, male patients were over-represented. Notably, Black/African American patients were under-represented in this study, comprising only 1.5% of the study population. Nevertheless, I do not believe that this disparity affects the efficacy and safety outcomes or the generalizability the study findings for an insulin product to the U.S. population.

Treatment Compliance and Rescue Medication Use

No specific study data were collected for the analysis of treatment compliance. Because this was a treat to target study with regular titration occurring during the study in subjects with T1D, there was no need for rescue medication.

Data Quality and Integrity

Dr. Tu, the statistical reviewer, found the submitted data adequate to conduct a statistical evaluation. She did not discover any notable data quality or analysis issues in the electronic submission that may impact the study results.

Efficacy Results

Primary and multiplicity adjusted endpoints:
The analyses for the primary and multiplicity adjusted endpoints are presented in Table 5. The FDA analyses conducted by Dr. Tu replicated the Applicant's results presented in the submission.

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

Treatment Arm	HbA1c (%), Lsmean (SE)			Lsmean Difference (Mealtime/Postmeal LY900014 vs Humalog) at Week 26 (95% CI)
	Baseline	Week 26	Change from Baseline at Week 26	

Humalog (N = 298)	7.81 (0.05)	7.87 (0.05)	0.06 (0.05)	
LY900014 (N = 280)	7.81 (0.05)	7.86 (0.05)	0.06 (0.05)	-0.01 (-0.15, 0.14)
LY900014 +20 (N = 138)	7.77 (0.07)	7.86 (0.08)	0.06 (0.08)	-0.00 (-0.18, 0.18)

Abbreviations: CI = confidence interval; Lsmean = Least-squares mean; SE = standard error.
Source: ITSB CSR table ITSB.5.2. (verified by FDA Statistical Reviewer)

Study ITSB demonstrated noninferiority of mealtime dosing with LY900014 to mealtime dosing with Humalog. The treatment difference for change from baseline in HbA1c after 26 weeks (LY900014-Humalog) was -0.01 (-0.15, 0.14), and the upper bound of the two-sided 95% CI was less than the prespecified NIM of 0.4%, thus establishing noninferiority. Given that the upper bound of the two-sided 95% CI was above zero, superiority of treatment with mealtime LY900014 to mealtime Humalog could not be demonstrated.

Noninferiority of postmeal dosing with LY900014 to mealtime dosing with Humalog was also established in Study ITSB: the treatment difference for change from baseline in HbA1c after 26 weeks (LY+20 - Humalog) was 0.00 (-0.18, 0.18), with the upper bound of the two-sided 95% CI less than the prespecified NIM of 0.4%.

Dr. Tu conducted a sensitivity analysis based on the method described in the *FDA Guidance for Industry: Non-inferiority Clinical Trials to Establish Effectiveness.* In this analysis, imputation of missing data under the inferiority null hypothesis was performed, i.e., the NI margin (0.4) was added to the imputed endpoints from the LY900014 arm. The analysis, as part of the one-way tipping point analysis result, shows a point estimate of 0.02 with its 95% CI (-0.13, 0.17), suggesting that NI still holds. The two-way tipping point analysis further corroborated the robustness of the primary analysis. A heatmap was generated based on the two-way tipping point analysis results. As presented in Figure 6, the primary result was overturned only when an implausible penalty (or benefit) was added to the treatment arm (or the control arm).

Reviewer comment: Study ITSB achieved its primary objective of demonstrating noninferiority of treatment between mealtime LY900014 and mealtime Humalog: the treatment difference for change from baseline in HbA1c after 26 weeks (LY900014-Humalog) was -0.01 (-0.15, 0.14), with the upper bound of the two-sided 95% CI below the prespecified NIM of 0.4%, thus establishing noninferiority. However, superiority could not be established for mealtime dosing of LY900014 as the upper bound of the 95% CI was above zero. The treatment difference for change from baseline HbA1c after 26 weeks for LY+20 compared to Humalog was 0 (-0.18, 0.18), which also established noninferiority with the upper bound of the two-sided 95% CI below the NIM of 0.4%.

Change in insulin doses:
Given that efficacy outcomes are dependent upon optimal insulin dose titration, interpretation of efficacy results requires the assessment for differences between treatment arms in insulin

dosing. Table 6 presents a summary and analysis of daily insulin doses (baseline and Week-26) and changes from baseline in daily insulin doses for basal, bolus, and total insulin by units per day (U/day) and units per kilogram per day (U/kg/day) across treatment arms.

Overall, insulin doses between the treatment arms appear comparable. There were no statistically significant treatment differences at baseline and at Week 26 for total daily insulin dose, total daily basal insulin dose, or total daily prandial insulin dose. Similarly, the prandial/total insulin dose ratios at baseline (Humalog, 53.4%; LY900014, 53.3%; and LY+20, 53.2%) and at Week 26 (Humalog, 53.2%; LY900014, 52.6%; and LY+20, 52.7%) were not noted to have any statistically significant treatment differences.

Table 6. Summary and Analysis of Insulin Dose (U/day and U/kg/day)

Time point		Treatment Group	n	LSM (SE)	LSM Diff at Week 26 A: LY900014 versus Humalog (95% CI), p-value B: LY900014+20 versus Humalog (95% CI), p-value C: LY900014+20 versus LY900014 (95% CI), p-value
Basal					
Baseline	U/day	Humalog	297	21.8 (0.72)	A: -0.8 (-2.8, 1.3), p=0.454
		LY900014	278	21.0 (0.74)	B: -1.1 (-3.6, 1.4), p=0.392
		LY900014+20	138	20.7 (1.05)	C: -0.3 (-2.8, 2.2), p=0.806
	U/kg/day	Humalog	297	0.41 (0.009)	A: -0.01 (-0.03, 0.02), p=0.565
		LY900014	278	0.41 (0.009)	B: -0.02 (-0.05, 0.01), p=0.235
		LY900014+20	138	0.39 (0.013)	C: -0.01 (-0.04, 0.02), p=0.475
Week 26 (Visit 15)	U/day	Humalog	283	23.5 (0.28)	A: 0.6 (-0.2, 1.4), p=0.130
		LY900014	264	24.1 (0.29)	B: 0.4 (-0.5, 1.4), p=0.404
		LY900014+20	132	23.9 (0.40)	C: -0.2 (-1.2, 0.8), p=0.693
	U/kg/day	Humalog	283	0.43 (0.004)	A: 0.01 (-0.00, 0.03), p=0.053
		LY900014	264	0.45 (0.005)	B: 0.01 (-0.01, 0.02), p=0.478
		LY900014+20	132	0.44 (0.007)	C: -0.01 (-0.02, 0.01), p=0.392
Bolus					
Baseline	U/day	Humalog	293	24.3 (0.77)	A: -0.7 (-2.9, 1.5), p=0.530
		LY900014	272	23.6 (0.80)	B: -1.1 (-3.8, 1.6), p=0.409
		LY900014+20	137	23.1 (1.13)	C: -0.4 (-3.1, 2.3), p=0.756
	U/kg/day	Humalog	293	0.48 (0.011)	A: -0.01 (-0.04, 0.02), p=0.369
		LY900014	272	0.47 (0.011)	B: -0.02 (-0.06, 0.01), p=0.193
		LY900014+20	137	0.45 (0.015)	C: -0.01 (-0.05, 0.03), p=0.573
Week 26 (Visit 15)	U/day	Humalog	279	26.8 (0.52)	A: -0.2 (-1.7, 1.2), p=0.748
		LY900014	256	26.6 (0.54)	B: -0.9 (-2.7, 0.9), p=0.325
		LY900014+20	131	25.9 (0.76)	C: -0.7 (-2.5, 1.2), p=0.477
	U/kg/day	Humalog	279	0.50 (0.009)	A: 0.01 (-0.02, 0.03), p=0.616
		LY900014	256	0.51 (0.009)	B: -0.01 (-0.04, 0.02), p=0.665
		LY900014+20	131	0.49 (0.013)	C: -0.01 (-0.04, 0.02), p=0.406
Total (basal + bolus)					
Baseline	U/day	Humalog	293	46.2 (1.32)	A: -1.9 (-5.6, 1.8), p=0.311
		LY900014	272	44.3 (1.37)	B: -2.4 (-6.9, 2.2), p=0.310
		LY900014+20	137	43.8 (1.92)	C: -0.4 (-5.1, 4.2), p=0.851
	U/kg/day	Humalog	293	0.89 (0.015)	A: -0.03 (-0.07, 0.02), p=0.238
		LY900014	272	0.87 (0.015)	B: -0.05 (-0.10, 0.00), p=0.076
		LY900014+20	137	0.85 (0.022)	C: -0.02 (-0.07, 0.03), p=0.420
Week 26 (Visit 15)	U/day	Humalog	279	50.3 (0.66)	A: 0.5 (-1.4, 2.3), p=0.625
		LY900014	256	50.7 (0.69)	B: -0.4 (-2.6, 1.9), p=0.758
		LY900014+20	131	49.9 (0.96)	C: -0.8 (-3.1, 1.5), p=0.485
	U/kg/day	Humalog	279	0.94 (0.011)	A: 0.02 (-0.01, 0.05), p=0.201
		LY900014	256	0.96 (0.011)	B: 0.00 (-0.04, 0.04), p=0.976
		LY900014+20	131	0.94 (0.016)	C: -0.02 (-0.06, 0.02), p=0.317

Abbreviations: CI= confidence interval; Diff= difference; LSM= least-squares mean; n= number of subjects; SE= standard error.

Source: ITSB CSR Table ITSB.5.5.

In addition to having comparable insulin doses at baseline and Week-26, each treatment arm should ideally achieve stable glycemia and, accordingly, should achieve a state of relative equilibrium for insulin doses for the 12 weeks prior to HbA1c assessment.

Table 7 summarizes the mean insulin doses (basal, bolus/prandial, and total) for each treatment arm by study visit. It is notable that most of the increase in both basal and prandial doses occurred during the titration period from baseline to Week-12. Although doses from Week-12 to Week-26 continued to increase, the incremental change was overall smaller during the latter half of the treatment period. The difference in mean total daily insulin dose between baseline and Week-12 visits for LY900014 and Humalog groups was greater than 4 units, whereas the difference between Week-12 and Week-26 visits was approximately 1.0 unit for both groups. The similarity suggests that the insulin dosing for the premeal treatment arms were similarly optimized and maintained during the study periods. The LY+20 group appeared to require more insulin dosage adjustments throughout the last half of the treatment period in comparison to the premeal dosing groups. The difference in mean total daily insulin dose for LY+20 group between baseline and Week-12 was approximately 3 units, whereas the difference between Week-12 and Week-26 was approximately 2.8 units. This finding suggests that the insulin dose and/or glycemia for the LY+20 treatment arm may not have been optimized prior to HbA1c assessment at Week-26.

Table 7. Summary of Mean Insulin Dose (U/day and U/kg/day) by Study Visit From Baseline to Week 26 Prior to Discontinuation of Investigational Product (IP) All Randomized Patients

	LY900014 (N=278)		LY+20 (N=138)		Humalog (N=297)	
Basal insulin dose	U	U/kg	U	U/kg	U	U/kg
Baseline	21.0	0.41	20.7	0.39	21.8	0.41
Week 4 (randomization)	21.5	0.42	21.3	0.42	22.0	0.42
Week 8	22.3	0.43	21.8	0.41	22.5	0.43
Week 12	22.7	0.43	22.3	0.42	23.1	0.43
Week 15	22.7	0.44	22.4	0.42	23.2	0.43
Week 18	23.0	0.44	22.8	0.42	23.4	0.43
Week 21	23.1	0.44	23.0	0.43	23.7	0.44
Week 24	23.5	0.45	23.7	0.43	23.9	0.44
Week 26	23.6	0.44	23.7	0.43	23.9	0.44
Bolus insulin dose	U	U/kg	U	U/kg	U	U/kg
Baseline	23.6	0.47	23.1	0.45	24.3	0.48
Week 4 (randomization)	25.1	0.50	24.2	0.47	25.8	0.51
Week 8	25.7	0.50	24.4	0.48	25.9	0.51
Week 12	26.4	0.51	24.6	0.48	27.0	0.52
Week 15	26.6	0.52	24.5	0.48	26.9	0.52
Week 18	26.8	0.52	25.7	0.49	27.3	0.52
Week 21	27.0	0.52	25.5	0.49	27.2	0.52
Week 24	26.3	0.51	25.4	0.48	27.7	0.52
Week 26	26.4	0.50	25.9	0.49	27.1	0.51

Total insulin dose	U	U/kg	U	U/kg	U	U/kg
Baseline	44.3	0.87	43.8	0.85	46.2	0.89
Week 4 (randomization)	46.4	0.92	45.6	0.88	47.9	0.93
Week 8	47.8	0.93	46.2	0.89	48.6	0.94
Week 12	49.0	0.94	46.8	0.89	50.2	0.96
Week 15	49.2	0.95	46.9	0.90	50.2	0.95
Week 18	49.7	0.95	48.5	0.91	50.9	0.95
Week 21	50.1	0.96	48.5	0.91	51.0	0.96
Week 24	49.7	0.96	49.1	0.92	51.8	0.97
Week 26	50.0	0.95	49.6	0.92	51.2	0.95

Source: ITSB CSR Adapted from Table ITSB.8.54.

Reviewer comment: The blinded premeal treatment arms had similar dosages and titration patterns. The unblinded LY+20 treatment arm appeared to require ongoing titration throughout the treatment period. Given that the investigators were granted flexibility in continuing to adjust insulin dosing throughout the treatment period, it is difficult to assess whether any differences noted were related to lack of adherence to the titration algorithm or due to reasons related to safety. Nevertheless, these insulin dose data do not suggest any differences in dosages or titration patterns which would favor the LY900014 treatment groups. Thus, these data support the validity of the demonstration of noninferiority of both LY900014 and LY+20 compared to Humalog on glycemic control.

Efficacy Results – Secondary and other relevant endpoints

Study ITSB did not include any prespecified key secondary endpoints. Endpoints concerning hypoglycemia and other safety-related topics are discussed in corresponding subsections of Section 8.

Proportion of patients achieving HbA1c targets:
Analysis of the proportion of patients achieving target HbA1c <7% and <7.5% are presented in Table 8. No statistical differences were found between the treatment arms and the control arm with respect to the proportions of subjects achieving the two HbA1c targets. These analyses are consistent with the results of the primary efficacy analyses.

Table 8. Proportion of Subjects Achieving HbA1c Targets at Week 26

	HbA1c < 7%		HbA1c < 7.5%	
Treatment (Number of Randomized Subjects)	Number (%) of Subjects Achieving the Target	Odds Ratio (Treatment/Control) (95% CI)	Number (%) of Subjects Achieving the Target	Odds Ratio (Treatment/Control) (95% CI)
Humalog (N = 298)	56 (20.00)		112 (40.00)	
LY900014 (N = 280)	57 (21.92)	1.23 (0.76, 2.00)	97 (37.31)	0.84 (0.55, 1.27)

LY900014 +20 (N = 138)	25 (19.08)	0.93 (0.49, 1.75)	43 (32.82)	0.62 (0.36, 1.08)

Source: Excerpted from FDA Statistical Review Table 6

Reviewer comment: LY+20 treatment arm had numerically smaller proportions of patients achieving the target HbA1c goals compared to LY00014 and Humalog in both categories. Although postmeal dosing of LY900014 demonstrated noninferiority to mealtime Humalog, these data suggest LY900014 is optimally dosed at mealtime.

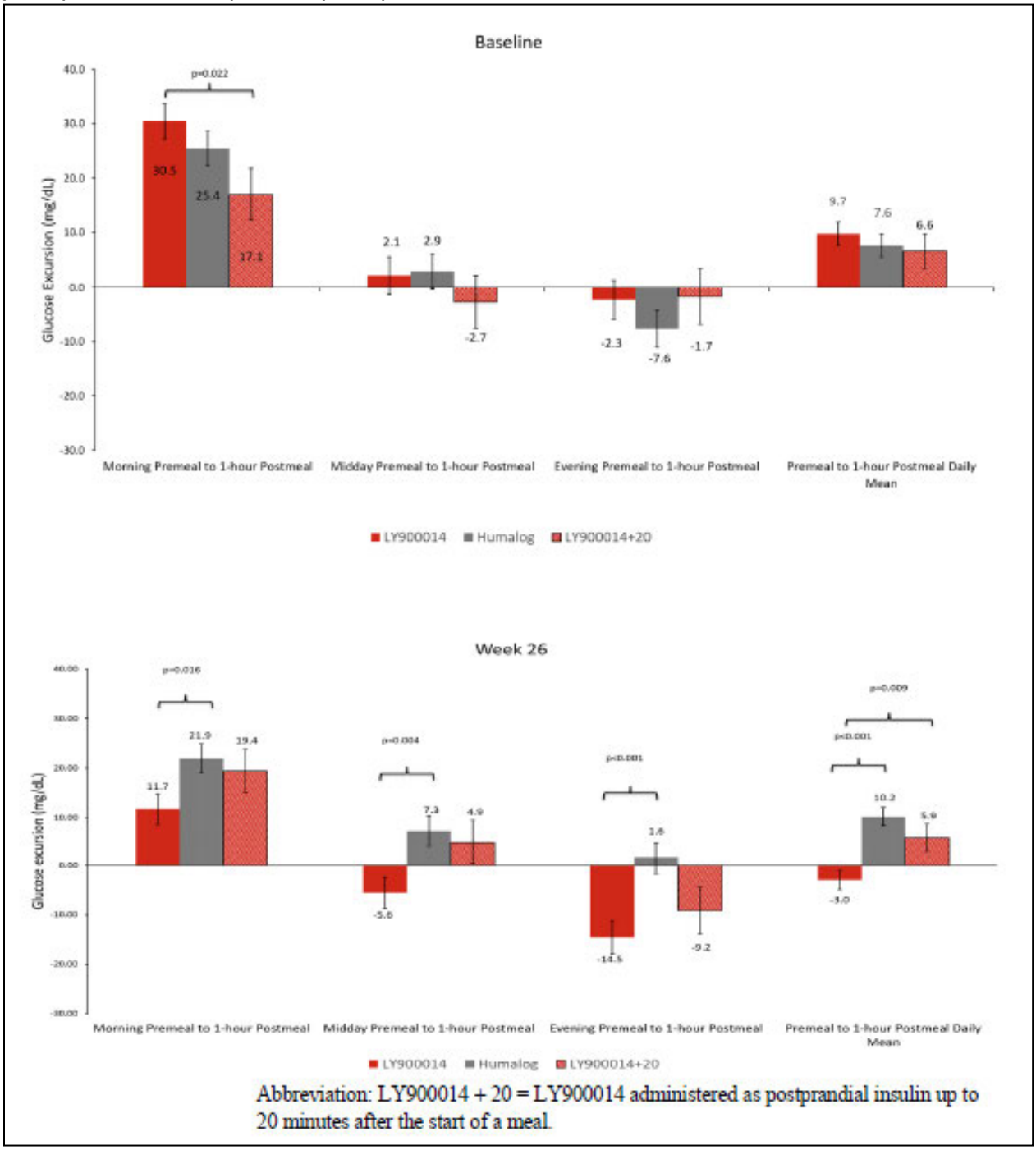
Change from baseline to Week 26 in 7-point SMBG values

A secondary objective of Study ITSB was to compare LY900014 and LY+ 20 to Humalog with respect to change in 7-point SMBG values after 26 weeks of treatment. Patients collected 3 separate 7-point SMBG profiles during the 2 weeks prior to Week 4 (randomization), Week 12, and Week 26.

At baseline, there were no significant differences between Humalog vs LY900014 or Humalog vs LY+20 treatment groups for PPG excursion (Figure 2). At Week 26, LY900014 group was statically significantly lower than Humalog at premeal to 1-hour postmeal excursion for morning, midday, and evening meals and for the premeal to 1-hour postmeal excursion daily mean.

Reviewer comment: The finding of greater reduction in postprandial glucose excursion with mealtime LY00014 vs Humalog at Week-26 compared to baseline is congruent with the data from the adult trials in patients with T1D and T2D. Although nominally statistically significant, the actual difference of the 1-hour postmeal PPG excursion daily mean from baseline was -11.3 mg/dL for LY900014 vs 1.9 mg/dL for Humalog. This modest difference in PPG excursion is of unknown clinical significance and is considered an exploratory endpoint; nevertheless, these data are supportive for the efficacy of LY900014.

Figure 2. Postprandial glucose excursions from self-monitored blood glucose at baseline (top panel) and Week 26 (bottom panel).



Source: ITSB Clinical Efficacy Summary Figure 2.7.3.4.

Dose/Dose Response

Dosing issues are discussed throughout the review.

Durability of Response / Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Subgroup analysis:
Dr. Tu's review included subgroup analyses on HbA1c (%) change from baseline for the following characteristics: sex (Male or Female), region (East Asia, Europe, North America, Other Region 1 [Brazil and Ireland], and Other Region 2 [Russia and Ukraine]), race (White and non-white), and age (1 to < 12 years and 12 to < 18 years) applying the same statistical method as the corresponding primary efficacy analysis (i.e., ANCOVA models with missing primary endpoints imputed based return-to-baseline). For each baseline characteristic, interactions between subgroups and treatment arms were tested. Additionally, Bayesian shrinkage analyses based on the sample estimates were performed. A summary of the sample estimates and shrinkage estimates of the treatment difference for HbA1c change from baseline at Week 26 is presented in Table 9.

Findings from the primary efficacy analyses (i.e., non-inferiority of the LY900014 to Humalog) generally hold within the subgroups. Although the upper bounds of the 95% CIs for East Asia, Other Region 1, and non-white cross the NI margin of 0.4, this is likely explained by the small sample sizes. The upper bound of the 95% CI for Europe stays below zero; however, the 95% credible interval of Europe, based on the shrinkage method, crosses zero by borrowing information from the other region categories. Thus, by Dr. Tu's analyses, no statistically significant subgroup-by-treatment effect was detected.

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

		LY900014 vs Humalog (N = 280)			**LY900014 +20 vs Humalog (N = 138)**		
Overall (95% CI)		**-0.01 (-0.15, 0.14)**			**-0.00 (-0.18, 0.18)**		
		Sample (95% CI)	**Shrinkage (95% CI)**	**n**	**Sample (95% CI)**	**Shrinkage (95% CI)**	**n**
Sex	Male	-0.03 (-0.22, 0.17)	-0.02 (-0.19, 0.16)	136	0.01 (-0.22, 0.25)	0.00 (-0.17, 0.18)	73
	Female	0.03 (-0.20, 0.25)	0.02 (-0.16, 0.19)	144	-0.03 (-0.30, 0.25)	-0.02 (-0.25, 0.21)	65
Region	East Asia	0.02 (-1.25, 1.29)	0.00 (-0.47, 0.50)	10	-0.23 (-1.69, 1.22)	-0.00 (-0.41, 0.35)	6

	Europe	-0.31 (-0.58, -0.04)	-0.16 (-0.46, 0.08)	84	0.08 (-0.25, 0.41)	0.03 (-0.20, 0.27)	39
	North America	0.05 (-0.23, 0.32)	0.02 (-0.20, 0.26)	77	-0.13 (-0.47, 0.21)	-0.03 (-0.30, 0.20)	36
	Other Region 1	0.23 (-0.19, 0.65)	0.08 (-0.22, 0.45)	35	-0.13 (-0.65, 0.40)	-0.01 (-0.34, 0.25)	18
	Other Region 2	0.13 (-0.10, 0.37)	0.06 (-0.16, 0.32)	74	0.13 (-0.17, 0.42)	0.05 (-0.15, 0.28)	39
Race*	White	-0.03 (-0.18, 0.11)	-0.02 (-0.21, 0.18)	256	0.00 (-0.17, 0.17)	0.00 (-0.19, 0.19)	126
	Non-White	0.27 (-0.52, 1.06)	0.10 (-0.38, 0.76)	22	0.03 (-1.09, 1.15)	0.01 (-0.72, 0.75)	9
Age	1 to < 12 years	0.02 (-0.19, 0.24)	0.01 (-0.16, 0.18)	98	0.13 (-0.13, 0.40)	0.07 (-0.17, 0.34)	50
	12 to < 18 years	-0.03 (-0.22, 0.17)	-0.02 (-0.19, 0.15)	182	-0.10 (-0.34, 0.13)	-0.07 (-0.26, 0.12)	88

*Two subjects from LY900014 and three subjects from LY900014 +20 had unreported race.
Source: Excerpted from FDA Statistical Review Table 9

The Applicant reported a significant treatment-by-race effect using six racial subgroups for race (p-value = 0.048). Given that White race was the predominate group, and no other race exceeded 10% of the full study population, Dr. Tu regrouped and reanalyzed race based on White vs Non-White, which resulted in a statistically insignificant treatment-by-race interaction (p-value = 0.25).

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Only the data from Study ITSB was included in this supplement to demonstrate efficacy; therefore, the subsections below are not applicable for this review.

7.1.1. Primary Endpoints

Not applicable.

7.1.2. Secondary and Other Endpoints

Not applicable.

7.1.3. Subpopulations

Not applicable.

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Results of Study ITSB demonstrated efficacy of LY900014 administered at mealtime and up to 20 minutes postmeal. Having an insulin product approved for dosing within 20 minutes after starting a meal is advantageous, particularly to pediatric patients with unpredictable dietary intake. Alternative timing of insulin dose offers convenience and flexibility when dosing prior to a meal is not convenient or is circumstantially delayed.

7.2.2. Other Relevant Benefits

The availability of another insulin approved for CSII condition of use is particularly beneficial to pediatric diabetic patients. Insulin pump therapy offers greater flexibility of meal timing and nutrient composition, as well as greater individualization of basal and prandial dosing than MDI due to the ability to deliver doses in smaller increments, which is particularly advantageous to insulin sensitive pediatric patients with diabetes.

7.3. Integrated Assessment of Effectiveness

The Applicant's proposed indication for Lyumjev is: *to improve glycemic control in adult and pediatric patients with diabetes mellitus*. In support of expanding the indication of LY900014 to pediatric patients with diabetes mellitus and the CSII condition of use, this sNDA included the results of two clinical studies: Study ITSA and Study ITSB.

Study ITSB was a 26-week, randomized, active controlled, treat-to-target, multinational trial that evaluated the efficacy of LY900014 in 716 pediatric patients with T1D. The primary objective of the study was to establish that LY900014 is noninferior to Humalog on glycemic control, as assessed by HbA1c, in patients 1 to < 18 years of age with T1D when administered as mealtime insulin in combination with basal insulin as part of an MDI regimen for 26 weeks. The prespecified noninferiority margin (NIM) was 0.4%. Multiplicity-adjusted objectives were to demonstrate noninferiority of LY900014 to Humalog on glycemic control when LY900014 is administered 20 minutes after the start of a meal and superiority of LY900014 to Humalog on glycemic when administered as mealtime insulin.

Study ITSB met its primary objective: the estimated treatment difference (LY900014 – Humalog) for reduction in HbA1c from baseline to week 26 was -0.01 (95% CI: -0.15, 0.14), establishing

noninferiority of LY900014 to Humalog as the upper bound of the two-sided 95% CI for treatment difference was less than the prespecified NIM of 0.4%. Similarly, Study ITSB met its first multiplicity adjusted secondary objective of demonstrating noninferiority of LY+20 to Humalog with and estimated treatment difference (LY+20 – Humalog) of 0.00 (95% CI: -0.18, 0.18). The superiority of mealtime LY900014 to Humalog was not achieved because the upper bound of the 95% CI was above 0. The results of the primary analyses were corroborated by the FDA statistical reviewer and were robust to sensitivity analysis using alternative missing data assumptions. Importantly, the analyses of changes in insulin doses between treatment arms over the treatment period did not show any statistically significant or clinically meaningful differences.

Study ITSA was a phase 1, randomized, double-blind, 2-period crossover study which compared the pharmacokinetic (PK) and pharmacodynamic (PD) profiles during a test meal of LY900014 and Humalog following SC administration of 0.2 U/kg in children (6 to <12 years), adolescents (12 to < 18 years) and adults (18 to <65 years) with T1D. In Part A of the study, patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus injection, and in Part B, patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus infusion via CSII.

Study ITSA demonstrated that the differences in PK profiles between LY900014 and Humalog following SC administration (via injection or via CSII bolus infusion) are similar in pediatric patients with T1D and adults with T1D. The similarity of the PK/PD relationship observed for LY900014 and Humalog administered via CSII bolus in adults with T1D is maintained in pediatric patients with T1D. In the context of the demonstrated safety and efficacy of LY900014 in pediatric patients with T1D based on the results of Study ITSB, the data from Study ITSA, support the extrapolation of the efficacy of CSII condition of use for LY900014 established from prior Study ITRO (the pivotal CSII trial in adults with T1D, reviewed with BLA 761109/S-003) to the pediatric T1D population.

To broaden the pediatric indication of LY900014 to include patients with T2D, FDA considered the totality of data from the LY900014 clinical and PK/PD investigations in pediatric and adult patients with T1D and adults with T2D. In addition to the observed data from the individual studies, FDA considered model-predicted insulin lispro PK profiles for patients with T2D based on the results from those studies: the models support a conclusion that LY900014 exerts glucose lowering effect comparable to Humalog across all age groups of patients with T2D (children, adolescents, and adults). These observations align with the PPG response observed in clinical pharmacology studies previously conducted in adults with T2D (Study ITRW, PK/PD study assessing mealtime and postmeal dosing in adults with T2D, reviewed with original submission of BLA 761109). Altogether, these data support the efficacy of LY900014 in pediatric patients with T2D.

In summary, the clinical data package submitted with this sBLA supports the efficacy of LY900014 in the broad pediatric diabetes population (i.e., T1D and T2D) and the CSII condition of use. Thus, the Applicant's proposed indication for LY900014 (i.e., indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus) is supported by the information in this submission.

8. Review of Safety

8.1. Safety Review Approach

Safety analyses were conducted on the Safety Population, which included all randomized patients who received at least 1 dose of the randomly assigned IP, with treatment group defined on the basis of the treatment the patients were assigned. During the Study ITSB, the safety data collected included treatment emergent adverse events (TEAEs), laboratory measures, vital signs, and immunogenicity. Additional assessments were performed based on topics of interest for an insulin product: hypoglycemia, systemic hypersensitivity reactions, and injection site reactions.

Using the FDA reviewer tools JMP, JMP Clinical and MAED, I analyzed the datasets for safety signals and performed additional subgroup analyses to explore differences between LY900014 and comparator, as described in the relevant subsections. Minor differences in the safety analyses between the Applicant's summaries and reviewer generated summaries did not change the overall conclusions of the findings.

The Applicant's safety analyses for this submission evaluated each treatment arm separately. For my analyses of serious adverse events (SAEs), treatment discontinuations and hypoglycemia, I analyzed the LY900014 and LY+20 treatment groups separately because the timing of IP dosing could contribute these events ; however, for the discussions pertaining to analyses of TEAEs and injection site AEs, I pooled the results of LY900014 and LY+20 treatment groups (All LY900014) to enhance the detection of an association between LY900014 and an AE and to discern the safety differences between LY900014 and Humalog.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A summary of exposure to the IP from randomization to Week 26 is provided in Table 10. A total of 418 patients received LY900014, approximately 85% of whom were exposed to LY900014 for 180 days or more. The exposure from first to last dose on IP in total patient-years was (b) (4) for LY900014, (b) (4) for Humalog, and (b) (4) for LY+20.

Table 10. Summary of Exposure to Investigational Product from Randomization to Week 26
All Randomized Patients

	Humalog (N=298) n (%)	LY900014 (N=280) n (%)	LY+20 (N=138) n (%)	Total (N=716) n (%)
Days of exposure				
> 0 to < 30 days	2 (0.7 %)	5 (1.8 %)	0	7 (1.0%)
≥ 30 to < 90 days	5 (1.7 %)	6 (2.1 %)	2 (1.4 %)	13 (1.8%)
≥ 90 to < 180 days	44 (14.8 %)	26 (9.3 %)	18 (13.0 %)	88 (12.3%)
≥ 180 days	247 (82.9 %)	243 (86.8 %)	118 (85.5 %)	608 (84.9%)

Abbreviations: N = number of patients in the analysis population; n = number of patients in the specified category;
Source: ITSB CSR Table ITSB.4.3.

8.2.2. Relevant characteristics of the safety population:

The characteristics of the safety population are presented in Table 4 in Section 6.1.2.

8.2.3. Adequacy of the safety database:

FDA agreed that Study ITSB was adequate in size and duration of exposure to provide the necessary data to evaluate the safety and efficacy Lyumjev in the pediatric population. Approximately 18% of the safety database is comprised of U.S. subjects. The safety population is predominantly white (> 90%) and fewer than 2% of the patients are Black or African American, and is limited to subjects with T1D. However, in my opinion, these imbalances should not affect the generalizability of the safety findings for an insulin product to the U.S. pediatric diabetes population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the overall submission was adequate to support a meaningful safety review. Key safety findings were reproducible and confirmed using the submitted datasets. Minor differences in the safety analyses between the Applicant's summaries and reviewer generated summaries did not change the overall conclusions of the findings.

8.3.2. Categorization of Adverse Events

Safety assessments included AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro. AEs were assessed at each study visit. AEs included a clinically significant worsening of a concomitant illness. Laboratory AEs included an abnormality which is clinically significant: an abnormality that suggests a disease and/or organ

toxicity and is of a severity that requires active management.

After the informed consent form (ICF) was signed, study site personnel recorded, via electronic data entry, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Any change in the condition and any new conditions were recorded as AEs. Investigators also recorded their assessment of the potential relatedness of each AE to protocol procedure and/or IP, via electronic data entry.

AEs that were newly reported after the first dose of study drug or were reported to worsen in severity from baseline were considered TEAEs. The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 lowest level term (LLT) was used in the treatment emergent assessment. The maximum severity for each LLT during the baseline period was used as baseline severity. The lead-in period was used as the baseline period.

An AE was defined as either a serious AE (SAE) or non-serious AE. SAEs are those that result in death, life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or important medical events based on medical judgement. In addition, severe hypoglycemia events were reported as SAEs in the Applicant's analyses. See Section Error! Reference source not found. for categorization of hypoglycemia.

8.3.3. Routine Clinical Tests

The schedule of study activities including routine clinical testing is summarized in Table 21 and discussed in Section Error! Reference source not found. under safety endpoints. The safety profile of LY900014 was assessed based on standard safety endpoints, including TEAEs, laboratory measures, vital signs, and immunogenicity. Additional assessments were performed based on topics of interest for an insulin product, including hypoglycemia, systemic hypersensitivity reactions, and injection site reactions.

Reviewer comment: The categorization of adverse events and safety assessment schedule were appropriate for an insulin product. Injection site reactions were collected as an AE of special interest.

8.4. Safety Results

Overview
An overview of the AEs reported during Study ITSB from randomization to safety follow-up are summarized in Table 11. Overall, the incidence of TEAEs was similar between study groups.

There were no significant differences in the mean changes in clinical laboratory values and vital signs between treatment arms.

Table 11. Summary of Adverse Events from Randomization to Safety Follow-up

	Humalog (N=298) n (%)	LY900014 (N=280) n (%)	LY+20 (N=138) n (%)
All TEAEs	144 (48.3)	131 (46.8)	52 (37.7)
Deaths	0	0	0
SAEs	12 (4.0)	6 (2.1)	2 (1.4)
AEs leading to discontinuation from study	0	2 (0.7)	0
AEs leading to discontinuation of treatment	0	2 (0.7)	0

Abbreviations: AE = adverse event; SAE = serious adverse event; N= number of subjects in analysis population; n= number of subjects with at least one adverse event per event type; TEAE = treatment-emergent adverse event.
Source: ITSB CSR Table ITSB.5.6.

8.4.1. Deaths

No deaths were reported in Study ITSB.

8.4.2. Serious Adverse Events

SAEs from randomization to safety follow-up by preferred term (PT) are presented in Error! Reference source not found.. The incidence of SAEs was overall low and numerically higher for the Humalog group. In total, 20 patients reported ≥ 1 SAE during the study: Humalog, 12 (4.0%), LY900014, 6 (1.4%), and LY+20, 2 (1.4%).

SAEs reported by more than one patient included the following:

- *Hypoglycaemia* (n=5): Humalog, 2 (0.7%); LY900014, 3 (1.1%); LY+20, 0
- *Diabetic ketoacidosis* (DKA) (n=3): Humalog, 0; LY900014, 2 (0.7%); LY+20, 1 (0.7%).

Review of the case narratives for the DKA events are summarized below:

- ✓ (b) (6): Patient is 14-year-old (b) (6) white female with T1D. She was randomized to LY+20 on (b) (6). On (b) (6) patient presented to ER with nausea, vomiting, abdominal pain, blood glucose of 361 mg/dL and ketoacidosis. Vomiting began at 23:28. Her last dose of IP was after her meal at 21:00. She was hospitalized and received hydration with 0.9% saline and insulin infusion with potassium supplementation. IP was withheld during the hospitalization. DKA resolved and patients IP was restarted on (b) (6) and patient was discharged (b) (6)
- ✓ (b) (6): Patient is 3-year-old (b) (6) white female with T1D who was randomized to LY900014 on (b) (6). On (b) (6) patient experienced abdominal pain, cough, and awoke with SMBG of 313 mg/dL and elevated ketone level on home testing. Patient's mother decided to treat the patient at home with oral hydration an administration of 1 unit of blinded IP SC every 3 hours. Blood glucose and ketone levels returned to normal, and

outcome was reported as recovered on (b) (6). The dose of IP was increased. Additional history revealed that patient's last dose of IP prior to DKA event was (b) (6) and principal investigator noted that event was related to non-adherence of IP according to prescribed guidelines.

- ✓ (b) (6): Patient is 14-year-old (b) (6) white male with T1D was randomized to LY900014 on (b) (6). On (b) (6), 79 days after beginning IP, the patient was hospitalized for DKA after having high blood sugar values in the morning. He had positive ketone testing, nausea and vomiting. Laboratory results at the time of the event included: glucose 391 mg/dL, potassium 5.5 mmol/L, sodium 138 mmol/L and pH 7.23 (no reference ranges provided). Patient received an insulin infusion. The patient had taken last dose of IP on (b) (6); however, he had forgotten a basal insulin injection on (b) (6). Patient recovered and was discharged on (b) (6). There was no change in study treatment as a result of the event.

Reviewer comment: AEs related to hypoglycemia are discussed in greater detail in Section 8.5.1. Of note, all 3 cases of DKA during Study ITSB occurred in patients receiving LY900014; however, review of case narratives suggest that missed doses of insulin (basal in 1 case and LY900014 in 1 case) contributed to the events in all but the first case. Therefore, in my opinion, this slight imbalance in DKA events between treatment groups does not raise clinical concern about the use of LY900014 in the pediatric population.

Table 12. Serious Adverse Events Preferred Term by Decreasing Frequency From Randomization to Safety Follow-up Safety Population

		Humalog (N=298)	LY900014 (N=280)	LY+20 (N=138)	
Preferred Term		n (%)	n (%)	n (%)	Total
Patients with ≥ 1 SAE		13 (4.4)	6 (2.1)	2 (1.4)	22(2.6)
Hypoglycaemia	0	3 (1.0)	3 (1.1)	0	6 (0.7)
Diabetic ketoacidosis	0	0	2 (0.7)	1 (0.7)	3 (0.4)
Abdominal pain	0	0	1 (0.4)	0	1 (0.1)
Anaphylactic reaction	0	1 (0.3)	0	0	1 (0.1)
Complicated appendicitis	0	0	0	1 (0.7)	1 (0.1)
Gastritis	0	1 (0.3)	0	0	1 (0.1)
Gastroenteritis	0	1 (0.3)	0	0	1 (0.1)
Headache	0	0	1 (0.4)	0	1 (0.1)
Hyperglycaemia	0	1 (0.3)	0	0	1 (0.1)
Hypoglycaemic coma	0	1 (0.3)	0	0	1 (0.1)
Macroglossia	0	1 (0.3)	0	0	1 (0.1)
Pilonidal cyst	0	1 (0.3)	0	0	1 (0.1)
Reactive gastropathy	0	1 (0.3)	0	0	1 (0.1)
Skin laceration	0	1 (0.3)	0	0	1 (0.1)
Spinal fracture	0	1 (0.3)	0	0	1 (0.1)
Upper respiratory tract infection	0	0	1 (0.4)	0	1 (0.1)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: None.
Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

AEs leading to treatment discontinuation were reported by 2 patients, both from the LY900014 treatment group.

- ✓ [redacted]: Patient is a 13-year-old [redacted] white female with T1D who experienced an AE of *injection site reaction* on [redacted], 16 days after starting treatment with LY900014. The AE was categorized as mild severity. The patient had no concomitant medications or other significant comorbidities. The patient discontinued treatment on the same day as the AE, and discontinued study participation on [redacted]. Event outcome was reported as resolving.
- ✓ [redacted]: Patient is a 12-year-old [redacted] white female with T1D who experienced an AE of *injection site pain* following the first dose of LY900014 on the day of randomization. The AE was categorized as moderate severity. The patient had not concomitant medications or other significant comorbidities. On the same day as the AE, the patient discontinued study treatment and 5 days later discontinued study participation. Event outcome was reported as resolved.

Reviewer comment: *Injection site reaction and injection site pain were the only AEs leading to treatment/study discontinuation and both occurred with LY900014 use. In total, these two cases of discontinuation due to injection site AEs represent less than 0.5% of the All LY900014 group. See Section 8.5.2 for additional discussion about TEAEs of injection site reactions.*

8.4.4. Significant Adverse Events

See Section 8.5 for discussion of other submission specific significant AEs.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A summary of TEAEs occurring in greater than 1% of patients receiving treatment with LY900014 is presented in Table 13. The proportion of patients with at least 1 TEAE was similar between the Humalog and the pooled treatment groups of patients receiving LY900014 (Humalog 55.4% vs All LY900014 48.6%).

The most frequently reported SOC for TEAEs were *Infections and infestations, Gastrointestinal disorders*, and *General disorders and administration site conditions*. The most frequently reported TEAEs occurring in at least 5% of patients in any treatment group were *nasopharyngitis* (10.5%) followed by *upper respiratory infection* (5.0%).

Overall, reporting of TEAEs was similar between treatment groups for each PT, with the exception of *injection site reaction* (Humalog 0.3% vs All LY900014 3.3%) and *injection site pain* (Humalog 0.3% vs All LY900014 1.4%). Injection site AEs are discussed in greater detail as an AE of special interest in Section 8.5.2.

Table 13. Treatment Emergent Adverse Events Occurring in at Least 1% of Patients Receiving LY900014 from Randomization to Safety Follow-Up Safety Population by System Organ Class and Preferred Term

	ALL LY900014 (N=418)	Humalog (N=298)	Total (N=716)
Any TEAE	203 (48.6)	165 (55.4)	368 (51.4)
TEAE by System Organ Class and Preferred Term			
Infections and infestations	140 (33.5)	110 (36.9)	250 (34.9)
Nasopharyngitis	48 (11.5)	27 (9.1)	75 (10.5)
Upper respiratory tract infection	20 (4.8)	16 (5.4)	36 (5.0)
Rhinitis	13 (3.1)	14 (4.7)	27 (3.8)
Pharyngitis	12 (2.9)	5 (1.7)	17 (2.4)
Respiratory tract infection	12 (2.9)	8 (2.7)	20 (2.8)
Tonsillitis	11 (2.6)	3 (1.0)	14 (2.0)
Influenza	9 (2.2)	9 (3.0)	18 (2.5)
Gastroenteritis	8 (1.9)	9 (3.0)	17 (2.4)
Respiratory tract infection viral	7 (1.7)	4 (1.3)	11 (1.5)
Sinusitis	6 (1.4)	2 (0.7)	8 (1.1)
Viral infection	6 (1.4)	3 (1.0)	9 (1.3)
Pharyngitis streptococcal	3 (0.7)	3 (1.0)	6 (0.8)
Gastrointestinal disorders	45 (10.8)	32 (10.7)	77 (10.8)
Vomiting	13 (3.1)	9 (3.0)	22 (3.1)
Abdominal pain	8 (1.9)	7 (2.3)	15 (2.1)
Abdominal pain upper	8 (1.9)	5 (1.7)	13 (1.8)
Diarrhoea	5 (1.2)	4 (1.3)	9 (1.3)
General disorders /administration site conditions	38 (9.1)	15 (5.0)	53 (7.4)
Injection site reaction	14 (3.3)	1 (0.3)	15 (2.1)
Injection site pain	6 (1.4)	1 (0.3)	7 (1.0)
Pyrexia	6 (1.4)	8 (2.7)	14 (2.0)
Respiratory, thoracic and mediastinal disorders	28 (6.7)	18 (6.0)	46 (6.4)
Oropharyngeal pain	9 (2.2)	5 (1.7)	14 (2.0)
Cough	7 (1.7)	3 (1.0)	10 (1.4)
Nervous system disorders	24 (5.7)	18 (6.0)	42 (5.9)
Headache	19 (4.5)	15 (5.0)	34 (4.7)
Metabolism and nutrition disorders	16 (3.8)	14 (4.7)	30 (4.2)
Hypoglycaemia	4 (1.0)	3 (1.0)	7 (1.0)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', STUDYID = 'I8B-MC-ITSB'.
Any TEAE - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'.
TEAE by SOC and PT - Dataset: Adverse Events; Filter: None; Percent Threshold: >= 1%.

8.4.6. Laboratory Findings

No clinically meaningful treatment differences were noted in laboratories during Study ITSB including hepatic, chemistry, and hematology tests. Accordingly, there were no significant treatment differences in the incidence of treatment-emergent abnormal laboratory values.

8.4.7. Vital Signs

The analyses of vital sign measurements and physical examination assessments detected no clinically meaningful findings related to safety in Study ITSB. The assessments and observations were comparable across treatment groups. For weight, BMI, and height assessments, change from baseline at Week 26 was significant for all treatment groups and was not considered adverse, given the pediatric study population.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were not collected during Study ITSB.

8.4.9. QT

ECGs were not performed routinely during Study ITSB and no AEs were related to QT changes were reported.

8.4.10. Immunogenicity

Development of antibodies with any new insulin therapy has the theoretical potential to lead to reduced drug exposure by neutralizing the effect of the drug, which may result in loss of glycemic efficacy or necessitate larger insulin doses to maintain glycemic control. Increased risk of hypersensitivity reactions, infusion site reactions and hypoglycemia are other concerns related to immunogenicity. Immunogenicity with LY900014 was analyzed in detail in the original BLA review of the pivotal MDI trial in adults with T1D. Although instances of treatment-induced and treatment-boosted treatment emergent anti-insulin lispro antibodies (ADA) were noted during the pivotal adult study, no associated adverse clinical sequelae such as loss of efficacy or increased safety risk were noted.

Immunogenicity in the pediatric program for LY900014 was assessed in Study ITSB by blood sampling, using a validated radioligand-binding assay, to determine ADA titers for all enrolled patients at baseline, prior to the first dose of IP. Subsequent samples for immunogenicity testing were collected as specified in the Schedule of Activities (Table 21).

Overall, 686 participants were evaluable for ADAs at baseline. Of these, 493 (71.9%) patients were positive for preexisting ADAs. Out of the 493 patients, 477 (96.8%) patients were positive for cross-reactive ADAs.

Congruent with the findings in the adult T1D study, postbaseline, the data showed no meaningful differences in immunogenicity between the treatment groups in Study ITSB (Table 14). Similarly, there were not meaningful differences between the treatment groups in cross-reactivity to native insulin. Furthermore, there were no clinically meaningful differences on insulin dose requirements, risk of hypersensitivity reactions, infusion site reactions or

hypoglycemia based upon treatment- emergent ADA (TEADA) status.

Table 14. Summary of Postbaseline ADA

Category	Humalog	LY900014	LY900014+20
TEADA evaluable, n	287	268	131
TEADA positive, n (%)	75 (26.1)	85 (31.7)	37 (28.2)
Treatment-induced ADA positive, n (%)[a]	27 (9.4)	31 (11.6)	20 (15.3)
Treatment-boosted ADA positive, n (%)[a]	48 (16.7)	54 (20.1)	17 (13.0)
Cross-reactive ADA to LY900014, n (%)[a]	65 (86.7)	70 (82.4)	33 (89.2)

Abbreviations: ADA = anti-drug antibody; n= number of subjects; TEADA = treatment-emergent ADA.
a Denominator = TEADA positive n value.
Source: ITSB CSR Table ITSB.5.29.

Reviewer comment: Congruent with the findings of the adult phase 3 studies, there were no meaningful differences in immunogenicity between LY900014 and Humalog treatment groups and there were no associated adverse clinical sequelae related to efficacy or safety were noted in the pediatric population with T1D.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hypoglycemia

During Study ITSB, whenever hypoglycemia was suspected, the patient (or parent/caregiver) was instructed to check BG with a study-provided BG meter, and record their BG value, the date and time, any associated symptoms, and the treatment administered in their study diary. All hypoglycemia events (severe and non-severe) were to be reported on the hypoglycemia electronic case report form (eCRF). All episodes of severe hypoglycemia were to be reported as SAEs on the AE eCRF page and on the SAE eCRF page. Episodes of hypoglycemia not meeting the criteria for severe hypoglycemia were not to be reported as an AE.

Hypoglycemia was described using the following definitions:

- Documented Glucose Alert: BG ≤70 mg/dL
- Documented Clinically Significant Hypoglycemia: event threshold BG <54 mg/dL
- Severe Hypoglycemia: event during which patients had an altered mental status and could not assist in their own care, may have been semiconscious or unconscious, or experienced coma with or without seizures, and the event required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose measurements may not have been available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal was considered sufficient evidence that the event was induced by a low BG concentration (BG ≤70 mg/dL).

  - As young children frequently require assistance with treatment of hypoglycemia even when not experiencing signs of altered mental status or cognitive impairment, the final determination of a severe hypoglycemia event, as defined above, was made by the investigator based on the medical need of the child to have required assistance (i.e., altered mental status or cognitive impairment) and was not predicated on the report of a child simply having received assistance. All episodes of severe hypoglycemia were reported as SAEs.
- Other Hypoglycemia:
  - Nocturnal hypoglycemia: event occurring between bedtime and waking
  - Non-nocturnal hypoglycemia: event occurring between waking and bedtime
  - Probable symptomatic hypoglycemia: event during which symptoms are present but BG measurement was not reported
  - Overall (total) hypoglycemia: combines all cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia) excluding the events of relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category.

For my review of safety, I look at the incidences and rates of severe hypoglycemia and clinically significant hypoglycemia events of < 54 mg/dL occurring with or without symptoms. Given the differing PK/PD profiles of LY900014 and Humalog, additional discussion of the differences in postdose hypoglycemia patterns between the Humalog and LY900014 and LY+20 groups is presented.

Severe Hypoglycemia
Incidence and Rate:
The incidence and rate of severe hypoglycemia events are summarized in Table 15. No statistically significant treatment differences in the incidence or rate were noted in either the lead-in period or treatment period (Weeks 0 to 26).

Table 15. Rate and Incidence of Severe Hypoglycemia

Treatment	Rate			Incidence		
	Mean (SD)	Aggregate Rate/100 Years	p-Value[a]	n (%)	Episodes	p-Value[b]
Lead-in Period (all patients treated with Humalog)						
Humalog (N=298)	3.95 (68.3)	4.44	0.959[c]	1 (0.3)	1	0.957[c]
LY900014 (N=280)	5.93 (99.2)	4.77	NC[d]	1 (0.4)	1	0.839[d]
LY900014+20 (N=138)	0	0	NC[e]	0	0	0.809[e]
Randomization to Week 26						
Humalog (N=298)	2.43 (25.3)	2.05	0.928[c]	3 (1.0)	3	0.929[c]
LY900014 (N=280)	2.07 (20.0)	2.20	NC[d]	3 (1.1)	3	0.414[d]
LY900014+20 (N=138)	0	0	NC[e]	0	0	0.389[e]

Abbreviations: n = number of patients with hypoglycemia; N = number of subjects in the population with baseline and postbaseline values at the specified time point; NC = not calculable; SD = standard deviation; vs = versus.

[a] p-Value is from empirical variance estimation for the event rate and is for comparison of aggregate rates.

[b] p-Value is from logistic regression model with term for treatment.

[c] LY900014 vs Humalog.

[d] LY900014+20 vs Humalog.

[e] LY900014+20 vs LY900014.

Source: ITSB CSR Table ITSB.5.10.

There were very few events of severe hypoglycemia during the treatment period of Study ITSB. A total of 6 patients (0.8%) reported 1 event of severe hypoglycemia each from randomization to Week 26:

- Humalog, n=3 patients (1.0%) (2 hypoglycemia; 1 hypoglycemic coma)
- LY900014, n=3 patients (1.1%) (3 hypoglycemia)
- LY900014+20, n=0 patients

Review of the case narratives for the LY900014 severe hypoglycemia events are summarized below:

- ✓ (b) (6): Patient is a 3-year-old (b) (6) white female with T1D. On (b) (6), the patient was randomized to LY900014. On (b) (6) at 8:00 AM, the patient's glucose value before the breakfast was 117 mg/dL. At 8:15 AM, the patient's mother administered 2.5 units of study drug, according to the carbohydrate count. The patient's mother was advised to give the study drug between 0-2 minutes before the meal, but she waited 15 minutes as she had done prior to randomization. The patient became lethargic and sleepy. The patient's FGM did not read the glucose value, and when the patient's mother checked using the study glucometer at 8:50 AM, the glucose value was 27 mg/dL. The patient was administered yogurt, candy and bread. The patient recovered. The patient did not have other hypoglycemic events during the day, and was hyperglycemic when he went to bed.

The outcome of the event was recovered (on the same day). No action taken with blinded study drug due to the event.

- ✓ [redacted]: Patient is an 8-year-old [redacted] white female with T1D. On [redacted], the patient was randomized to LY900014. On [redacted] at 09:10 AM, the patient's mother administered 7 units of basal insulin. At 9:48 PM, the patients mother administered 4.5 units of prandial insulin instead of 3.5 units. The patient also had dinner at the same time and ate less than expected and felt drowsiness and weakness. At 9:48 PM, the patient's blood glucose was 382 mg/dl. At 10:30 PM, the patient went to bed. On [redacted] at 12:43 AM, the patient was awakened and felt weak. BG was 31 mg/dl. The patient was drowsy and weak. The mother reported the patient likely had reduction in the level of consciousness, but without fainting. The mother treated patient with oral sugar syrup and after a few minutes there was an important improvement in the patient condition. The patient recovered from the event. No change with blinded study drug as a result of the event.
- ✓ [redacted] Patient is an 8-year-old [redacted] white male with T1D. On [redacted], the patient was randomized to LY900014. Concomitant insulin degludec 6 units was taken on [redacted]. On [redacted] patient received LY900014 twice: on an unspecified time, he received 3 U and at 6:26 PM, patient measured his blood glucose of 300 mg/dL then injected 5 U and left his home without eating. At 7:54 PM, patient informed his parents that he was feeling sick and BG was 27 mg/dL. Patient became very sleepy, asthenic, he was unable to treat himself. His parents treated him with a glass of soda and patient started to feel better after a few minutes with a BG of 60 mg/dL. With this episode, insulin was administered by the patient himself, without parental supervision. Patient recovered from the SAE and there was no change in blinded study drug therapy, as the patient recovered after parental assistance and did not experience further events.

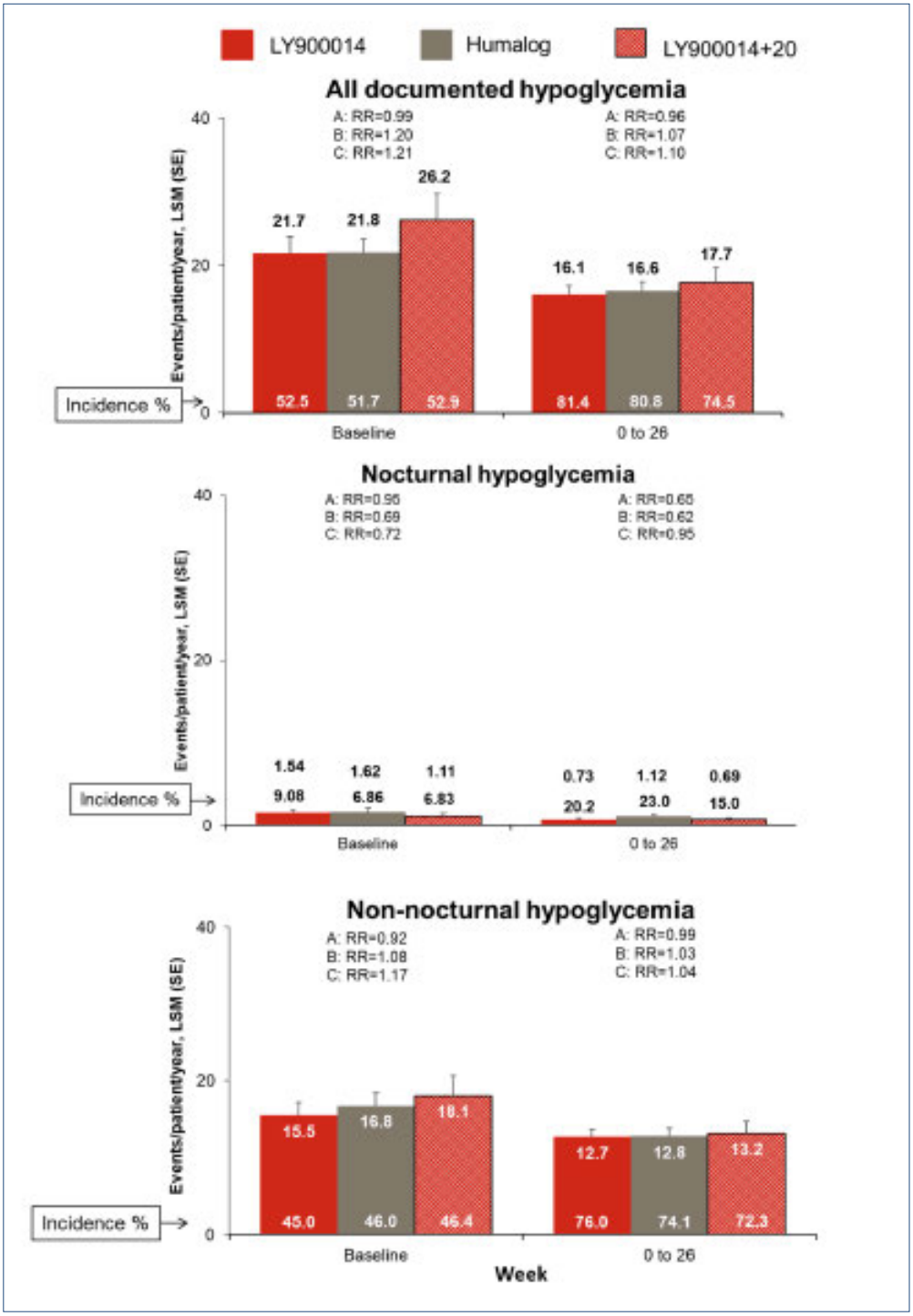
Reviewer comment: *Review of the case narratives of severe hypoglycemia with LY900014 reveal that patient or caregiver error contributed to all 3 events.*

All Documented Hypoglycemia BG < 54 mg/dL
Incidence and Rate:
The incidence and rate for each category of hypoglycemia with BG <54 mg/dL at baseline and during the treatment period are illustrated in Figure 3. There were no significant differences between treatment groups for either the incidences or rates of all documented, nocturnal, and non-nocturnal hypoglycemia at baseline and from Weeks 0 to 26 for BG<54 mg/dL.

Reviewer comment: *At baseline, the LY+20 group is noted to have a numerically higher rate of all documented hypoglycemia compared to LY900014 and Humalog groups; however, following randomization, the LY+20 groups had rates of hypoglycemia very similar to the other treatment groups. Not surprisingly, during the treatment period, when prandial insulin doses were being*

actively titrated by investigators based on SMBG, the incidences of all categories of hypoglycemia increased while the rates decreased for all treatment groups.

Figure 3. Rate and incidence of hypoglycemia BG <54 mg/dL for baseline and Weeks 0 to 26



Abbreviations: A = LY900014/Humalog; B = LY900014+20/Humalog; BG = blood glucose; C = LY900014+20/LY900014; LSM = least-squares mean; RR = relative rate; SE = standard error.
Source: ITSB CSR Figure ITSB.5.5

Postdose Hypoglycemia
Hypoglycemia was captured and analyzed for each treatment group relative to the time of most recent mealtime dose given (postdose) i.e., at mealtime for LY900014 and Humalog and 20 minutes after meal for LY+20. The rate and incidence of all documented symptomatic and asymptomatic postdose hypoglycemia with BG <54 mg/dL by time period (≤1 hour, ≤ 2 hour, ≤ 4 hour, and > 4hour) at baseline and during the treatment period are illustrated in
Incidence:
For Weeks 0 to 26, for BG <54 mg/dL, there were significant differences for the incidence of postdose hypoglycemia for LY900014 group compared to Humalog for the following time points:

- ≤1 hour after the start of the prandial dose between LY900014 and Humalog (n=103 [36.8%] versus n=79 [26.5%], p=0.008), and
- ≤2 hours after the start of the prandial dose between LY900014 and Humalog (n=178 [63.6%] versus n=161 [54.0%], p=0.020).

Rate:
The rate of hypoglycemia < 54 mg/dL for Weeks 0 to 26 was higher for the LY900014 and LY+20 treatment arms compared to Humalog for the following timepoints:

- LY900014 versus Humalog at ≤2 hours after the start of the prandial dose (RR [95% CI] = 1.33 [1.02, 1.72], p=0.034)
- LY900014+20 and Humalog at ≤4 hours after the start of the prandial dose (RR [95% CI] = 1.33 [1.01, 1.74], p=0.040)
- LY900014+20 versus LY900014 at >2 to ≤4 hours after the start of the prandial dose (RR [95% CI] = 1.45 [1.05, 2.01], p=0.025).

Reviewer comment: *As previously noted in Figure 3, the incidence and rate of all documented hypoglycemia <54 mg/dL (including non-nocturnal and nocturnal) during Weeks 0 to 26 for the LY900014 group were comparable to those of Humalog. The subsequent analysis of the timing hypoglycemia, relative to dosing, demonstrate LY900014 group has higher incidence and rate of hypoglycemia than Humalog group at postdose timepoints (≤1 hour and ≤2 hours). For LY+20 group, the rate of hypoglycemia is greater than Humalog at a later postdose timepoint (≤ 4 hours). For timepoints > 4 hours, Humalog had higher rate and incidence of hypoglycemia than LY900014 and LY+20. Thus, the timing pattern of postmeal hypoglycemia is consistent with the faster time-action profile of LY900014 than Humalog.*

Figure 4.

Baseline:
Incidence:

At baseline, there were no significant differences in the incidence of postdose hypoglycemia of < 54 mg/dL between any treatment group.

Rate:
The rate of hypoglycemia < 54 mg/dL at baseline was significantly higher for the LY+20 group compared to the other groups for the following time points:

- LY900014+20 versus Humalog at ≤2 hours after the start of the prandial dose (RR [95%CI] = 1.55 [1.03, 2.33], p=0.034)
- LY900014+20 versus LY900014 at ≤2 hours after the start of the prandial dose (RR [95% CI] =1.73 [1.14, 2.64], p=0.010), and
- LY900014+20 versus LY900014 at ≤4 hours after the start of the prandial dose (RR [95% CI] = 1.47 [1.04, 2.09], p=0.030).

Reviewer comment: *Of note, events at baseline were those occurring during lead-in period, when all patients were treated with Humalog. Congruent with the information on Figure 3, the LY+20 group had a similar incidence but a higher rate of hypoglycemia at baseline than the Humalog and LY900014 groups. Not surprisingly, Humalog administration postmeal results in higher rates of postdose hypoglycemia (≤2 hours and ≤4 hours).*

Weeks 0 to 26:
Incidence:
For Weeks 0 to 26, for BG <54 mg/dL, there were significant differences for the incidence of postdose hypoglycemia for LY900014 group compared to Humalog for the following time points:

- ≤1 hour after the start of the prandial dose between LY900014 and Humalog (n=103 [36.8%] versus n=79 [26.5%], p=0.008), and
- ≤2 hours after the start of the prandial dose between LY900014 and Humalog (n=178 [63.6%] versus n=161 [54.0%], p=0.020).

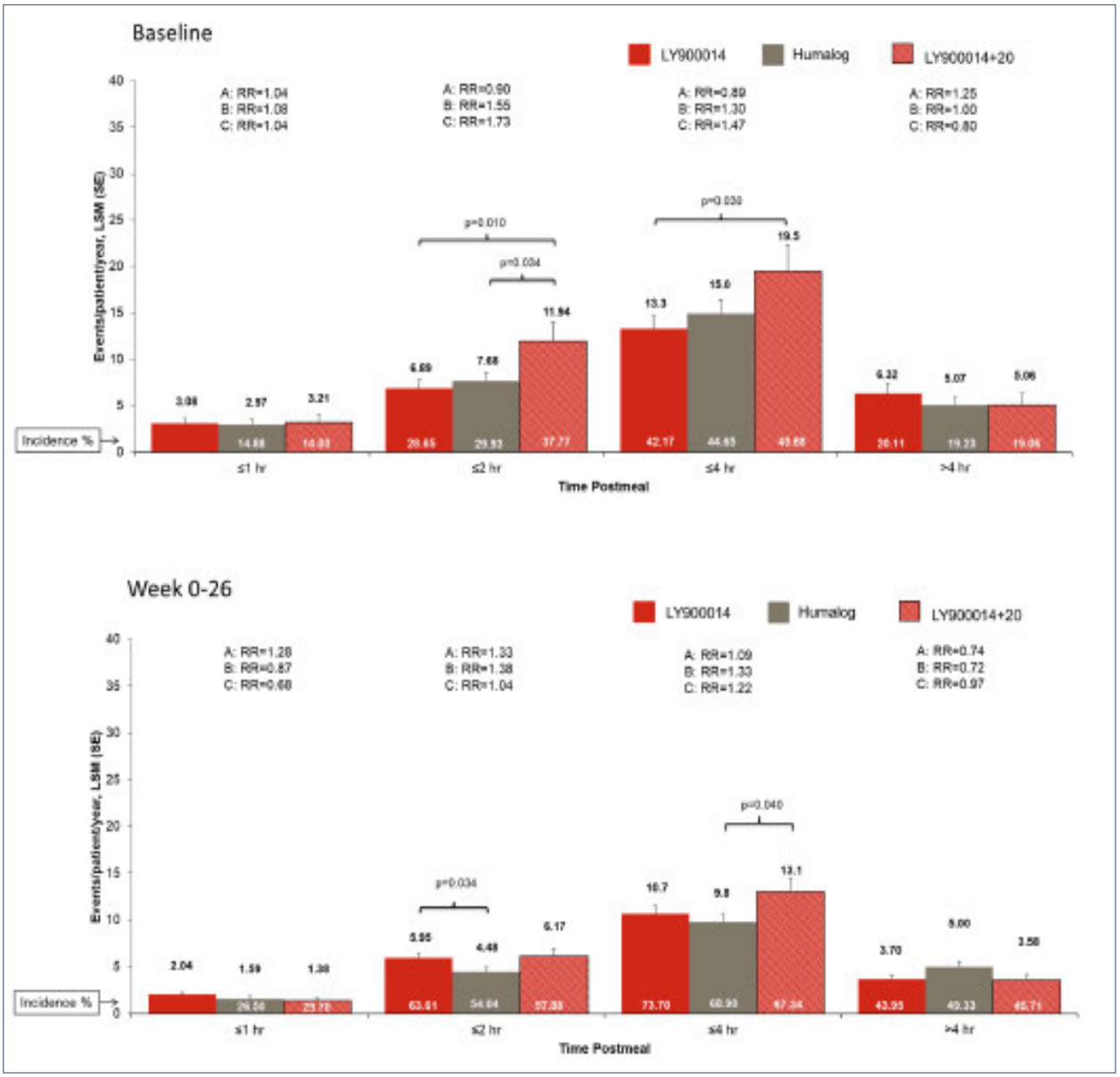
Rate:
The rate of hypoglycemia < 54 mg/dL for Weeks 0 to 26 was higher for the LY900014 and LY+20 treatment arms compared to Humalog for the following timepoints:

- LY900014 versus Humalog at ≤2 hours after the start of the prandial dose (RR [95% CI] = 1.33 [1.02, 1.72], p=0.034)
- LY900014+20 and Humalog at ≤4 hours after the start of the prandial dose (RR [95% CI] = 1.33 [1.01, 1.74], p=0.040)
- LY900014+20 versus LY900014 at >2 to ≤4 hours after the start of the prandial dose (RR [95% CI] = 1.45 [1.05, 2.01], p=0.025).

Reviewer comment: *As previously noted in Figure 3, the incidence and rate of all documented hypoglycemia <54 mg/dL (including non-nocturnal and nocturnal) during Weeks 0 to 26 for the LY900014 group were comparable to those of Humalog. The subsequent analysis of the timing*

hypoglycemia, relative to dosing, demonstrate LY900014 group has higher incidence and rate of hypoglycemia than Humalog group at postdose timepoints (≤1 hour and ≤2 hours). For LY+20 group, the rate of hypoglycemia is greater than Humalog at a later postdose timepoint (≤ 4 hours). For timepoints > 4 hours, Humalog had higher rate and incidence of hypoglycemia than LY900014 and LY+20. Thus, the timing pattern of postmeal hypoglycemia is consistent with the faster time-action profile of LY900014 than Humalog.

Figure 4. Rate and incidence of documented postdose hypoglycemia BG <54 mg/dL for baseline (top panel) and Weeks 0 to 26 (bottom panel)



Abbreviations: A = LY900014/Humalog; B = LY900014+20/Humalog; BG = blood glucose; C = LY900014+20/LY900014; LSM = least-squares mean; RR = relative rate; SE = standard error.
Source: ITSB CSR Figure ITSB.5.7.

Subgroup analysis for hypoglycemia:
At baseline for BG <54 mg/dL, there were no statistically significant treatment-by-subgroup interactions for Age Group 1 (1 to <12 years and 12 to < 18 years), Age Group 2 (1 to <6, 6 to <12, and 12 to <18 years), HbA1c stratum, region, type of basal insulin, prandial insulin dosing plan, personal CGM/FGM use, and TEADA status.

During the treatment period, the treatment-by-subgroup interaction was not significant for any subgroup except Age Group 2.

- For Age Groups 6 to <12 and 12 to <18, there were no significant differences between treatment groups.
- As summarized in Table 16, for Age Group 1 to <6 years, there were significantly higher rates of hypoglycemia for the following:
  - LY900014 versus Humalog at Weeks 0 to 26 (RR [95% CI] = 3.37 [1.68, 6.76], p=0.001)
  - LY900014+20 versus Humalog at Weeks 0 to 26 (RR [95% CI] = 4.19 [1.87, 9.36], p=0.001)

Table 16. Summary and Analysis of Event Rate for Hypoglycemia < 54 mg/dL for Age Group 1-<6 years Weeks 0-26

Variable Analyzed: All Documented Hypoglycemia with Glucose < 54 mg/dL when Pooled Age Group 2 = 1-<6

Time Point / Treatment	N	Mean (SD)	(Min, Med, Max)	LSMean (SE) *a*b
0<wk<=26				
Humalog	7	8.1 (6.23)	(0.0, 9.9, 16.0)	8.9 (2.04)
LY900014	10	30.1 (24.85)	(0.0,26.0, 86.5)	30.1 (7.46)
LY900014 Postmeal	10	37.4 (39.34)	(0.0,33.7,132.5)	37.4 (11.80)

Pairwise Comparison (A vs B)	Relative Rate (Treatment A/B) (95% CI)*a*b	p-value*a*b
LY900014 vs Humalog	3.37 (1.68, 6.76)	0.001
LY900014 Postmeal vs Humalog	4.19 (1.87, 9.36)	0.001
LY900014 Postmeal vs LY900014	1.24 (0.54, 2.84)	0.594

Source: ITSB CSR Table ITSB.8.111.

Table 17. Incidence of All Documented Hypoglycemia <54 mg/dL for Age Group 1-<6 years Weeks 0 - 26

Variable Analyzed: All Documented Hypoglycemia with Glucose < 54 mg/dL when Pooled Age Group 1 = 1-<12

Time Point / Treatment	N	n (%)	Number of Episodes	LSMean (SE) (%)*a*b
Baseline				
Humalog	105	57 (54.29)	184	54.25 (4.862)
LY900014	98	54 (55.10)	182	55.05 (5.025)
LY900014 Postmeal	50	29 (58.00)	110	57.84 (6.984)
Total	253	140 (55.34)	476	

Pairwise Comparison (A vs B)	Odds Ratio (Treatment A/B) (95% CI)*a*b	p-value*a*b
LY900014 vs Humalog	1.03 (0.59,1.80)	0.908
LY900014 Postmeal vs Humalog	1.16 (0.59,2.28)	0.674
LY900014 Postmeal vs LY900014	1.12 (0.56,2.23)	0.746

Source: ITSB CSR Table ITSB.8.125.

As summarized in Table 4, the youngest age group comprised a very small proportion of the safety population (n=27, 3.8%) and a greater proportion of those patients were treated with LY900014 (Humalog, 7; LY900014, 10; LY+20, 10). It is notable that the although the rates of hypoglycemia for the LY900014 treatment arms were unfavorable compared to Humalog, the incidence of hypoglycemia was comparable between treatment groups: [Humalog(85.7%); LY900014 (90%); LY+20 (90%)] (see Table 17) .

To further investigate the disparity between the incidence and rate of hypoglycemia in the subset of patients treated with LY900014 and LY+20 in the youngest age range, I analyzed the number of hypoglycemic episodes occurring in individual patients for all treatment groups. As summarized in **Table 18**, both the LY900014 and LY+20 treatment groups had proportionately more patients experiencing over 20 episodes of hypoglycemia (shaded in gray) than the Humalog treatment group (All LY900014, 50% vs Humalog, 33%) and conversely, patients with fewer than 10 episodes comprised the majority of the Humalog group and substantially less of the LY900014 treated patients (All LY900014, 11% vs Humalog 67%).

Table 18. Summary of Individual Patients and Number of BG< 54mg/dL Events from Weeks 0 to 26 for Age Group 1-<6 years by Treatment Group

Treatment Group	Patient ID	Number of events
Humalog		
	(b) (6)	50
		33
		8
		8
		5
		2
LY900014		
	(b) (6)	80
		73
		47
		34
		15
		14
		13
		13
		2
		1
LY+20		
	(b) (6)	66
		32
		30
		26
		25
		18
		16
		12

Source: Reviewer generated using JMP adhypo.xpt and adsl.xpt

Reviewer comment: The higher relative rate of hypoglycemia with LY900014 and LY+20 treatment groups compared to Humalog in the youngest and most vulnerable subgroup is concerning. However, it is reassuring that the incidence of hypoglycemia is noted to be comparable between all treatment groups for this age bracket and that no significant differences in the rate or incidence of hypoglycemia were noted for any other age groups on subgroup analysis. It is possible that more patients who are less susceptible to hypoglycemia may have been randomized to the Humalog group than to All LY900014 groups, given the imbalance in the proportions of patients with hypoglycemia events greater than 20 and fewer than 10 did not favor All LY900014. In addition, the number of subjects in this age group is very small (n=27), and therefore it is possible that this imbalance may have occurred by chance. For these reasons, I do not believe any definitive conclusions can be drawn from this isolated imbalance noted from this subgroup analysis.

8.5.2. Injection Site Reactions

Injection site reactions are a frequently reported adverse reaction associated with insulin products. During the adult clinical development program, injection site reactions occurred with greater frequency in the All LY90004 group compared to Humalog group. The most likely reason for this imbalance is the use of novel absorption enhancing excipients in LY900014: treprostinil to enhance local vasodilation and sodium citrate to enhance vascular permeability. At each office visit of Study ITSB, the skin surrounding the injection sites was assessed and the presence and severity of injection site erythema, induration, pain, pruritis, and edema were recorded in an eCRF. A customized MedDRA query (CMQ) was also used by the Applicant to identify potential injection site reactions. Table 19 provides a summary of the incidence of events by PT.

Reviewer comment: There are a few more cases of injection site reactions for all treatment groups, including Humalog, from my analysis summarized on Table 19 (data generated using JMP Clinical) than what is presented by the Applicant; however, the minor differences do not change the overall conclusions discussed in this section.

A total of 34 patients (4.7%) experienced at least 1 TEAE of injection site reactions, with a total of 46 injection site reaction events. The incidence of injection site reactions was greater in the LY900014 group than Humalog:

- Humalog: n=8 (2.7%)
- LY900014: n=22 (7.9%)
- LY900014+20: n=4 (2.9%)
- All LY900014: n=26 (6.2%)

Injection site AEs occurred in 6.2% of All LY900014 patients and severity was reported as mild (5.7%) or moderate (0.5%) in all cases. The most commonly reported events PTs experienced by patients in the LY900014 groups included the following:

- *injection site reaction* (LY900014, n=12; LY900014+20, n=2)
- *injection site erythema* (LY900014=4; LY900014+20=0), and
- *injection site pain* (LY900014, n=5; LY900014+20, n=1).

Two patients in the LY900014 treatment group (0.48%) discontinued study treatment due to AEs of *injection site reaction* (mild) and *injection site pain* (moderate). Section 8.4.3. contains a detailed review of these two cases.

Table 19. Incidence of Potential Treatment-Emergent Injection Site Reactions Using Customized MedDRA Query Randomization to Safety Follow-up

	HUMALOG N=298 n (%)	All LY900014 N=418 n (%)		LY900014 N= 280 n (%)	LY +20 N=138 n (%)
TOTAL	12 (4.0%)	29 (6.9)		25 (8.9%)	5 (3.6%)
Preferred Term					
Injection site reaction	1 (0.3)	14 (3.3)		12 (4.3)	2 (1.4)
Injection site pain	1 (0.3)	6 (1.4)		5 (1.8)	1 (0.7)
Injection site erythema	1 (0.3)	4 (1.0)		4 (1.4)	0
Lipohypertrophy	4 (1.3)	1 (0.2)		1 (0.4)	0
Injection site induration	2 (0.7)	0		0	0
Lipodystrophy acquired	3 (1.0)	0		0	0
Injection site bruising	0	2 (0.5)		1 (0.4)	1 (0.7)
Injection site mass	0	1 (0.2)		0	1 (0.7)
Injection site pruritus	0	1 (0.2)		1 (0.4)	0

Source: Reviewer generated using JMP Clinical

Reviewer comment: *The higher incidence of injection site reactions with treatment with LY900014 compared to Humalog (All LY900014, 6.2% vs Humalog, 2.7%) in Study ITSB was similar to the findings from the adult trials in patients with T1D and T2D. The incidence of injection site reactions from MDI and infusion site reactions from CSII use with LY900014 in adults was, 2.7% and 37.7%, respectively. It is notable that for the pediatric patient population, the incidence of injection site reactions for All LY900014 was 6.2%, approximately 2.5 times higher than observed in adults. For this reason, it is quite possible that pediatric patients will also have a higher incidence of infusion site reactions compared to the adult population with CSII use. Of note, in the adult CSII studies, none of the infusion site reactions were reported as SAEs, the vast majority were mild or moderate in severity, and fewer than 3.3% of treatment discontinuations were related to these AEs.*

Table 20 summarizes the incidence of injection site reactions by age groups and treatment groups (Humalog vs All LY900014). A small percentage (4%) of subjects composed the youngest

subgroup under 6 years of age and fewer of these patients were randomized to Humalog [Humalog 7/298 (2.3%) vs LY 20/418 (4.5%)]. The majority of subjects were age 12 and older (65%), and the remaining patients (~30%) were in the middle subgroup of 6 to 11 years of age.

The underrepresentation of the lowest age group does not permit a proper age-related comparison; however, injection site AEs reported with ALL LY900014 are distributed across all age groups. Review of the case narratives of these events revealed that the BMI of these patients ranged between 14 and 31.6 kg/m^2. Total insulin doses ranged between 14-88 units/day. These wide variations do not suggest a dose-related relationship to the occurrence of injection site AEs.

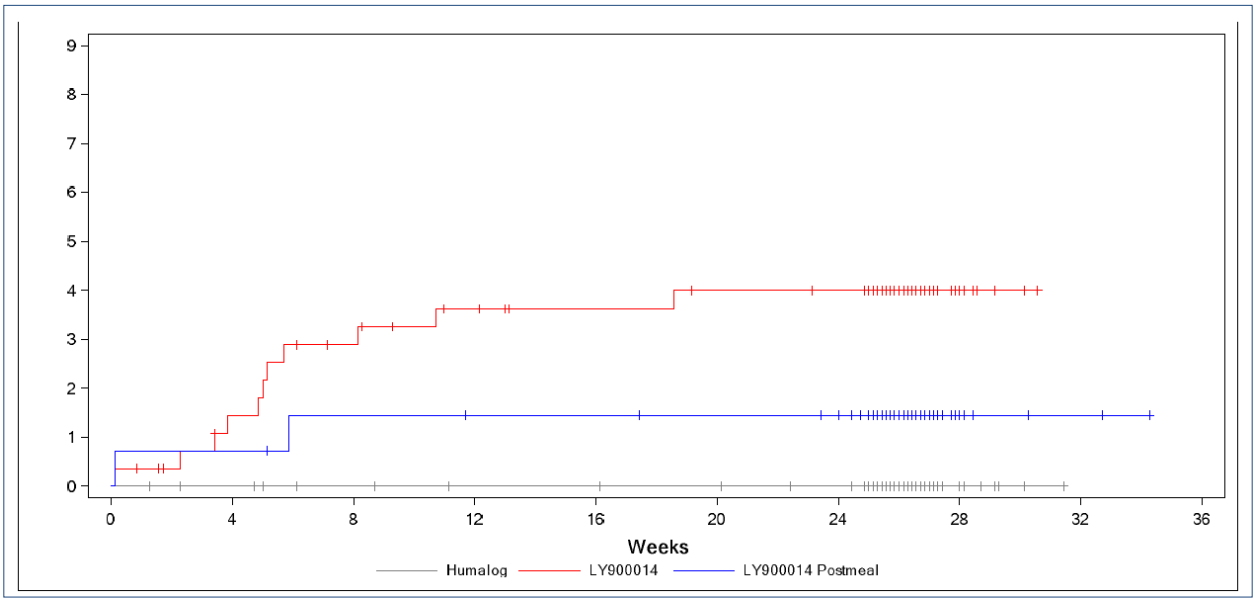
Table 20. Incidence of Injection Site Related AEs by Age Groups

	HUMALOG N= 298			All LY900014 N = 418		
Age Group years n (%)	1 to < 6 7 (2.3)	6 to < 12 98 (32.9)	12 to < 18 193 (64.8)	1 to < 6 20 (4.5)	6 to < 12 128 (30.6)	12 to < 18 270 (64.6)
PREFERRED TERM						
Injection site reaction	0	1 (1.0)	0	0	5 (3.9)	9 (3.3)
Injection site pain	0	0	1 (0.5)	2 (10.0)	1 (0.8)	3 (1.1)
Injection site erythema	0	0	1 (0.5)	0	1 (0.8)	3 (1.1)
Lipohypertrophy	0	1 (1.0)	3 (1.6)	0	1 (0.8)	0
Lipodystrophy acquired	0	1 (1.0)	2 (1.0)	0	0	0
Injection site induration	0	0	2 (1.0)	0	0	0
Injection site bruising	0	0	0	0	1 (0.8)	1 (0.4)
Injection site mass	0	0	0	0	0	1 (0.4)
Injection site pruritus	0	0	0	0	0	1 (0.4)
TOTAL	0	3 (3.0)	9 (4.7)	2 (10.0)	9 (7.0)	18 (6.7)

Source: Reviewer generated using JMP Clinical

Review of the Kaplan-Meier time to event curve Figure 5 shows the majority of injection site reaction events occurred within 6 weeks of treatment initiation with LY900014.

Figure 5. Time to first treatment-emergent adverse event occurring in **≥1%** of patients from randomization to safety follow-up in Study ITSB (infusion site reaction)



Abbreviations: LY900014 Postmeal = LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal.
N = number of subjects in analysis population; n = number of subjects with events meeting specified.
The plot is based on Kaplan-Meier Survival Analysis.
Raw data incidence: Humalog: N = 298, n(%) = 0(0.0%); LY900014: N = 280, n(%) = 11(3.9%); LY900014 Postmeal: N = 138, n(%) = 2(1.4%)
Source: ITSB CSR Figure ITSB.8.1.

Reviewer comment: In summary, consistent with the findings from the adult clinical program, the incidence of injection site reactions is higher with LY900014 than with Humalog in pediatric patients. The majority of events were categorized as mild or moderate in severity and rarely resulted in treatment discontinuation. Time-to-event analysis suggests that most patients who experience an AE of injection site reaction do so within 6 weeks of treatment initiation. The additional analyses of the available pediatric data did not discern any common characteristics of patients susceptible to developing the AE of injection site reaction with LY900014 use.

PK/PD data from Study ITSA is provided to expand the CSII condition of use of Lyumjev to the pediatric population. Dr. Tello's concludes in her consult for CDRH that the potential device-related risks with LY900014 for pediatric patients do not appear to be greater than Humalog, based on review of the adult CSII subset with lowest TDI doses; however, given that the incidence of infusion site reactions was higher than injection site reactions in the adult population, it is reasonable to assume that this will also be the case for the pediatric population. Of note, the infusion site reactions from the adult trials were not SAEs and the analyses of the data from the lower TDI doses were unable to identify any particular patient characteristics which could help a HCP prevent, monitor for, or mitigate risk. Therefore, the PI for LY900014 should be adequately labeled to inform prescribers and patients (caretakers) of the potential increased risk of infusion site reaction when initiating treatment.

8.5.3. Hypersensitivity

In order to identify potential hypersensitivity reactions from the spontaneously reported AEs, the following standardized MeDRA queries (SMQs) were run by the Applicant: anaphylactic reaction, angioedema, and hypersensitivity.

The results of these queries revealed that a total of 2.6% of patients treated with LY900014 and 3.7% of patients treated with Humalog experienced potential hypersensitivity reactions. None of these hypersensitivity reactions were serious and none lead to treatment or study discontinuation. *Rhinitis allergic* (0.7%), *dermatitis allergic* (0.2%), *rash* (0.5%), and *hypersensitivity* (0.5%) were the most common events reported with LY900014 treatment. The proportion of LY900014-treated patients reporting these events was less than or equal to the proportion of Humalog-treated patients, with the exception of the PT of hypersensitivity (Humalog, 0.3% and LY900014, 0.5%).

8.6. Safety Analyses by Demographic Subgroups

The overall incidence of TEAEs and TEAEs reported by at least 3% of LY900014-treated patients in Study ITSB were analyzed by subgroups of patients' demographic and baseline disease characteristics (age group, gender, race, ethnicity, BMI-by-age, height-by-age) to evaluate possible differences in response to study drug. No treatment-by-subgroup interactions were noted for any of these subgroups analyzed. Similarly, the incidence of TEAEs were analyzed by geographic region (East Asia, Europe, North America, Brazil and Israel, Russian Federation and Ukraine) and there were no treatment-by-subgroup interactions for region, indicating no significant differential treatment effect on incidence of TEAEs across regions. Subgroup analyses for clinically significant hypoglycemia is discussed in Section 8.5.1.

8.7. Specific Safety Studies/Clinical Trials

Not applicable for this submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable for this submission.

8.8.2. Human Reproduction and Pregnancy

The safety of LY900014 in patients with diabetes during pregnancy and in the post-delivery period has not been studied systematically. Patients who became pregnant in previous adult phase 3 studies evaluating LY900014 were discontinued from study drug and/or from the study and monitored for safety follow-up. No pregnancies were reported during Study ITSB.

8.8.3. Pediatrics and Assessment of Effects on Growth

Study ITSB was completed to fulfill FDA issued PMR 3874-1. Safety evaluations for this study included analysis of weight, height, and BMI as well as vital signs at scheduled visits over 26 weeks (see Table 21). The analyses detected no clinically meaningful findings in the vital sign measurements and physical examination assessments, or other observations related to safety in this study. The assessments and observations were comparable across treatment groups. For weight, BMI, and height assessments, change from baseline at Week 26 was significant for all treatment groups (summary and analysis of these parameters at scheduled visits are presented in Table ITSB.8.153. of CSR).

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Neither Lyumjev nor the pharmacologic class of human insulin has a known profile as a drug of abuse. No rebound effect has been observed for insulin products. There were no reported instances of intended drug abuse in the LY900014 clinical program. Excess insulin administration, including LY900014, may cause hypoglycemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes involving coma, seizure, or neurologic impairment may be treated with glucagon or concentrated intravenous glucose. See Section 8.5.1 for additional discussion about hypoglycemia.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

On April 6, 2022, the Applicant submitted the 120 Day Safety Update of any post-marketing reports and literature search relevant for Lyumjev. As of the cutoff date of March 14, 2022, no new clinical studies with pediatric patients have been initiated or completed. Lyumjev has not received approval for pediatric use in any foreign countries and no new label language specific to pediatric use has been added to date. Postmarketing data monitored through routine pharmacovigilance activities have not identified any new or significant safety signals and no additional risk minimization activities have been proposed.

The Periodic Safety Update Report /Periodic Benefit-Risk Evaluation Report (PSUR-PBRER) for Lyumjev covering the reporting period May 1, 2021, through April 30, 2022, estimates that cumulatively, there was an estimated (b) (4) patient-years of exposure to LY900014 worldwide through April 30, 2022. During the time period covered by the reports, no significant actions have been taken or are proposed for safety reasons.

8.9.2. Expectations on Safety in the Postmarket Setting

Lyumjev has been approved in the U.S. since June 15, 2020, with the indication to improve glycemic control in adults with diabetes mellitus and the CSII condition of use was approved on August 13, 2021. The data from the adult clinical program for Lyumjev is generally comparable to Humalog in terms of safety; however, the incidences of infusion site reactions and infusion site pain were higher for Lyumjev via CSII than MDI. These ARs were reported as mild or moderate in severity in the majority of cases, resolved with discontinuation of treatment, and resulted in discontinuation of therapy in 3.3% of study subjects. None of these ARs were reported as SAEs.

Although the PK/PD findings from Study ITSA allow for the expansion of CSII condition of use to the diabetic pediatric population, the safety of continued delivery via CSII in the pediatric population is an uncertainty. I expect the safety profile of Lyumjev administered via CSII in the pediatric diabetics will be similar to that observed in adults, i.e., that the incidence of infusion site reactions via CSII will likely be higher than injection site reactions via MDI. Given that injection site reactions in the pediatric population presented similarly to adults in clinical trials (i.e., mostly mild to moderate in severity, resolving with discontinuation, and necessitating therapeutic discontinuation in very few patients), I have no reason to suspect that the clinical presentation of infusion site reactions in the pediatric population would differ from what has been observed in adults with diabetes. Additionally, insulin pump therapy offers the benefit of greater flexibility of meal timing and nutrient composition, as well as greater individualization of incremental basal and prandial dosing than MDI, which is particularly advantageous in the insulin sensitive pediatric patients. Thus, in my opinion, the benefit-risk profile of CSII condition of use with Lyumjev remains favorable for the diabetic pediatric population.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by other disciplines at the time of this review.

8.10. Integrated Assessment of Safety

The safety data collected from pediatric diabetes clinical program do not indicate a change to the safety profile of LY900014 previously established in adult patients with diabetes. The safety of LY900014 appears similar to Humalog. The active ingredient in LY900014, insulin lispro, has been used in Humalog for over 20 years in adult and pediatric patients with diabetes and has a well-known safety profile. The main difference noted in AEs appear to be related to the excipients in LY900014, including AEs directly attributable to the excipients (e.g., injection site reactions) and differences related to the impact of the excipients on the time-action profile of insulin lispro.

During Study ITSB, no deaths occurred and the incidence of SAEs (Table 12) was low and numerically higher for Humalog (4.0%) compared to LY900014 (1.4%) and LY+20 (1.4%). SAEs most commonly reported were *hypoglycaemia* and *DKA*. A total of 6 patients (0.8%) reported 1

event of severe hypoglycemia each with equal numbers in LY900014 (n=3) and Humalog (n=3) groups. Three cases of DKA occurred during Study ITSB, all in patients receiving LY900014; however, case narratives reveal that errors related to missed doses of insulin contributed to 2 of the 3 cases, thus no safety concern is raised based on this slight imbalance.

The hypoglycemia safety profile for LY900014 was also found to be similar to Humalog. No significant differences between treatment groups were noted for either the incidences or rates of all documented hypoglycemia, nocturnal hypoglycemia, and non-nocturnal hypoglycemia (BG < 54 mg/dL) (Figure 3). Additionally, when hypoglycemia BG <54 mg/dL was analyzed relative to the time of the most recent dose, the differences in rates and incidences of hypoglycemia between treatment groups predictably correlated with the time action profile of the insulin and dosing, i.e., LY900014 group had greater hypoglycemia at timepoints ≤ 2 hours, LY+20 at timepoints >2 and ≤ 4 hours, and Humalog at timepoints > 4 hours.

The incidence of TEAEs was similar between Humalog and All LY900014 (Table 13). The most frequently reported TEAEs occurring in at least 5% of patients in any treatment group were *nasopharyngitis* (10.5%) followed by *upper respiratory infection* (5.0%). Overall, reporting of TEAEs was similar between treatment groups for each PT, with the exception of *injection site reaction* (Humalog 0.3% vs All LY900014 3.3%) and *injection site pain* (Humalog 0.3% vs All LY900014 1.4%). Injection site AEs occurred in 6.2% of All LY900014 group compared to 2.7% of Humalog group; however, the severity was reported as mild (5.7%) or moderate (0.5%) in all cases and less than 0.5% of patients receiving LY900014 discontinued treatment due to AEs related to injection site reactions.

In summary, the pediatric safety data from Study ITSB is comparable to the safety profile for LY900014 established from the pivotal adult T1D trial and is included in the current label. From a safety perspective, the reassuring findings of LY900014 demonstrated in pediatric patients with T1D also support a favorable benefit-risk profile for LY900014 use in the T2D population, because clinically, AEs with LY900014, such as hypoglycemia, would be more likely to occur with insulin dependent patients who are more insulin sensitive due to less endogenous insulin secretion. The PK/PD data from Study ITSA support the efficacy of the CSII condition of use of LY900014; however, the safety of continued delivery via CSII in the pediatric population is an uncertainty. Safety data from the adult CSII program for LY900014 found the occurrence of infusion site reactions to be greater than injection site reaction with MDI use. Reassuringly, no infusion site reactions were reported as SAEs, the majority of cases were mild or moderate in severity and reversible with cessation of the infusion, and fewer than 4% of cases necessitated therapeutic discontinuation. In total, the benefit-risk profile of LY900014 remains favorable for the pediatric population; however, the labeling should apprise HCPs and patients of the potential increased risk of infusion site reactions. For recommended labeling, see Section 10.1.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened, and no external consultations were obtained for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling recommendations have been included throughout the review. With respect to the inclusion of information pertaining to injection site reactions, the Applicant added incidence of these events from Study ITSB into Section 6.1 (Adverse Reactions: Clinical Trials Experience) of the PI. As discussed in previous sections, the potential for higher risk of infusion site reactions with CSII condition of use is important information to relay to HCP prescribing Lyumjev to pediatric patients. Because no pediatric clinical trial data for CSII administration for Lyumjev are available, the review team considered adding a statement to inform HCP of the risk of this potential AR into Section 5 (Warnings and Precautions) or Section 8.4 (Use in Specific Populations: Pediatric Use) of the PI.

Per the *Guidance for Industry- Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format*[2] *(October 2011),* the *Warnings and Precautions* section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management.

[2] https://www.fda.gov/media/71866/download

Per the *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling Guidance for Industry*[3] *(March 2019),* the *Pediatric Use* subsection must also include information related to the safe and effective pediatric use of the drug with cross references to other section of labeling as appropriate, such as any differences between pediatric and adult responses to the drug.

The analysis of the data from the Lyumjev CSII clinical program has shown that although infusion site reactions are common, they have not resulted in any cases of serious adverse events and they resulted in treatment discontinuation in less than 3% of cases. In addition, there have been no particular patient or clinical characteristics identified which could help an HCP prevent, monitor for, or mitigate the risk of infusion site reaction. For these reasons, the review team, with concurrence of the Labeling Policy team, determined that section 8.4 would be the most appropriate place to include information about the higher potential risk of infusion site reactions than injection site reactions. The proposed edits from the review team are included into the label below in blue text:

8.4 Pediatric Use

The safety and effectiveness of LYUMJEV to improve glycemic control in pediatric patients with diabetes mellitus have been established. Use of LYUMJEV for this indication is supported by evidence from an adequate and well-controlled study in 716 pediatric patients with type 1 diabetes mellitus aged 1 year and older, and from studies in adult and pediatric patients with diabetes mellitus *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

LYUMJEV-treated pediatric patients reported a higher incidence of subcutaneous injection site-related reactions compared to LYUMJEV-treated adults *[see Adverse Reactions (6.1)].* It is expected that LYUMJEV-treated pediatric patients who receive continuous subcutaneous insulin infusion (CSII) are more likely to have infusion site-related adverse reactions than those who receive subcutaneous injections *[see Adverse Reactions (6.1)]*. Monitor injection and infusion sites closely when initiating therapy with LYUMJEV in pediatric patients. If persistent injection or infusion site reactions occur, discontinue LYUMJEV and initiate therapy with an alternative insulin.

[3] https://www.fda.gov/media/84949/download

The Labeling Policy Team also update sections of the PI to align with the recently published labeling guidance documents *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling--Content and Format (February 2022)*[4] and *Geriatric Information in Human Prescription Drug and Biological Product Labeling (September 2020)*[5].

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategy is recommended for this product.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or postmarketing commitments are recommended as a result of review of this submission.

13. Appendices

13.1. References

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[4] https://www.fda.gov/media/155871/download
[5] https://www.fda.gov/media/142162/download

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13.2. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the *Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators*[6]. In accordance with 21 CFR 54.4, the Applicant has submitted Form 3454 for Study ITSB. None of the investigators who participated in this trial had disclosable financial interests/arrangements.

Covered Clinical Study (Name and/or Number): ITSB

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 337		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

[6] https://www.fda.gov/media/85293/download

influenced by the outcome of the study: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Supplemental Tables and Figures

Appears this way on original

Table 21. Study ITSB Schedule of Activities

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[b]
eCRF Visit Number	**1**	**2**	**3[c]**	**4**	**5[c]**	**6[c]**	**7**	**8[c]**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14[c]**	**15**	**801[d]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Informed Consent/Assent (if applicable)	X																
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient eligibility review	X	X															
Randomization				X													
Clinical Assessments																	
Demographic data[e]	X																
Medical history, preexisting conditions	X																
Previous diabetes therapy	X																
Record Personal CGM/FGM use (yes/no)				X													
Height[f]	X			X						X					X		X
Weight	X	X		X			X			X		X			X		X
Vital signs (sitting SBP, DBP, and HR)[g]	X	X		X			X			X		X			X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and product complaints		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Focused physical exam (including skin evaluation)[h]	X	X		X			X			X		X			X		X
Basal insulin dose assessment[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Basal insulin dose titration[j]		X	X	X	X	X	X	X	X	X							

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[b]
eCRF Visit Number	**1**	**2**	**3[c]**	**4**	**5[c]**	**6[c]**	**7**	**8[c]**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14[c]**	**15**	**801[d]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Prandial insulin dose assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Prandial insulin dose titration[i]				X	X	X	X	X	X	X							
Ancillary Supplies/Diaries/IP																	
Dispense blood glucose meter and ancillary supplies and complete training[k,l]		X		X			X			X		X					
Diabetes education and nutrition counseling[l]		X															
Dispense study diaries and complete training[l]		X		X			X			X		X					
Collect study diaries				X			X			X		X			X		X
Dispense IP		X		X			X			X		X					
Train on collecting 4- and 7-point SMBG profiles[m]		X															
Remind patient of 7-point SMBG requirements			X						X					X			
Review and discuss SMBG (and/or CGM/FGM) and hypoglycemia data from patient study diary				X			X			X		X			X		
Discuss SMBG (and/or CGM/FGM) and hypoglycemia data with patient			X		X	X		X	X		X		X	X			
Review/discuss only severe hypo data after completion of study treatment																X	

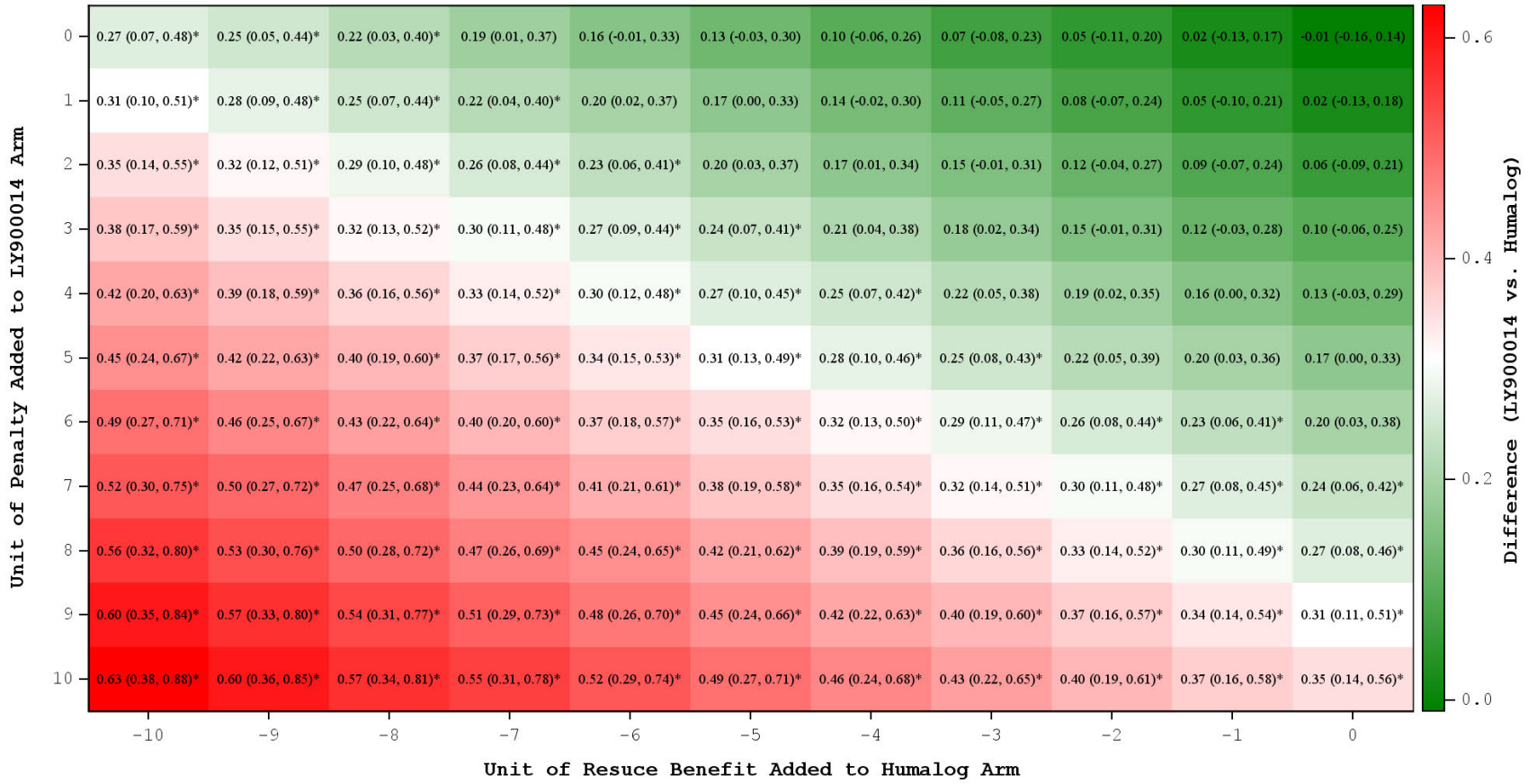
	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[b]
eCRF Visit Number	**1**	**2**	**3[c]**	**4**	**5[c]**	**6[c]**	**7**	**8[c]**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14[c]**	**15**	**801[d]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Patient returns unused study drug or open-label Humalog supplies				X			X			X		X			X		X
Drug accountability log				X			X			X		X			X		X
Laboratory Assessments																	
Pregnancy test, serum/urine (applicable females only)[n]	X			X													
Urinalysis (screening)	X																
HbA1c	X			X			X			X					X		X
Clinical chemistry	X														X		X
Hematology	X														X		X
Antilispro antibodies	X			X			X			X					X		X

Abbreviations: DBP = diastolic blood pressure; eCRF = electronic case report form; ED = early discontinuation; HbA1c = hemoglobin A1c; HR = heart rate; IP = investigational product; IWRS = interactive web-response system; SBP = systolic blood pressure; SMBG = self-monitored blood glucose; WHO = World Health Organization.

a. Patients who rescreen will start at Visit 1.
b. Randomized patients who decide to discontinue will be asked to return for the ED visit. If a patient discontinues during an office visit that visit may be treated as the ED visit. If a patient discontinues via telephone, they will be asked to return for the ED visit.
c. Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.
d. V801 will be a telephone visit; this visit can become an office visit.
e. Medical history to include investigator review of immunization status with patient and caregiver.
f. In order to obtain accurate measurements, length should be measured using an infantometer and height should be measured using a stadiometer (WHO Child Growth Standards).
g. Blood pressure measurements should be determined correctly, using the appropriate-sized cuff for the child's age and with the child seated and relaxed.
h. A qualified medical professional must perform a medical assessment at each site visit. During each office visit, the skin surrounding the injection sites should be assessed.
i. Basal insulin dose assessment should be made during the lead-in period and as needed during the study.
j. Basal insulin should be adjusted during the lead-in period so as to achieve or maintain BG targets with a focus on the prebreakfast BG. Prandial insulin should be titrated with an emphasis during the first 12 weeks after randomization in order to reach optimal dosing and achieve BG targets. Adjustment of basal and prandial insulin doses may continue throughout the 26-week treatment period in order to achieve or maintain glycemic targets based on changes in lifestyle, individual circumstances or for safety reasons.
k. Glucose monitoring supplies will be dispensed at each office visit, as needed.
l. Initial training at Visit 2 may include diabetes education and nutrition counseling. Appropriate site personnel will administer training and education using locally approved diabetes education/training materials or other materials provided by the sponsor. Patients may be provided abbreviated training and education at visits following Visit 2, as appropriate.
m. Patients who wear personal CGM/FGM approved for dosing decisions may be trained to use their sensor data for 4-point BG values and record in diary or download the BGs for investigator review.
n. Serum pregnancy test must be performed in female patients of childbearing potential (see inclusion criterion [9]) at Visit 1 followed by a urine pregnancy test within 24 hours prior to IP exposure at randomization (Visit 4) and at other times at the investigator's discretion. When required per local regulations and/or institutional guidelines, local pregnancy testing will occur at mandatory times during the study treatment period.

Source: Protocol ITSB (b) Table ITSB.1.

Figure 6. Heatmap for Two-Way Tipping Point Analysis for Primary Efficacy Analysis



Note: Each unit on marked on the x-axis and y-axis equals 0.5. The value in each cell is the mean difference (95% CI) in HbA1c (%) change from baseline between LY900014 and Humalog. Asterisks indicate that the primary result is tipped.
Source: Excerpted from FDA Statistical Review Figure 2

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