CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761109Orig1s000

SUMMARY REVIEW

CDTL Review and
Division Summary Memo for Regulatory Action

Date	June 15, 2020
From	Patrick Archdeacon, M.D.
BLA #	76109
Applicant	Eli Lilly and Company
Date of Submission Receipt	August 15, 2019
PDUFA Goal Date	June 15, 2020
(Proposed) Non-proprietary name	Insulin lispro-aabc
(Proposed) Trade name	Lyumjev
Dosage forms / Strength	Solution for sc injection: 100 units/mL in 10 mL vial, 3 mL cartridge, 3 mL pre-filled pen 200 units/mL in 3 mL pre-filled pen
Proposed Indication	To improve glycemic control in adults with diabetes mellitus
Recommended Action	Approval
Recommended Indication/Population	To improve glycemic control in adults with diabetes mellitus

1. Introduction

This document contains the 'Summary Basis for Regulatory Action' memo for the original Biologics License Application (BLA) 761109, received August 15, 2019, submitted under the 351(a) regulatory pathway for marketing approval of Lyumjev (insulin lispro-aabc) to improve glycemic control in adults with diabetes mellitus.

This memo references the following documents/sources:

Subject	Author(s)	Date
Office of Biotechnology Products	Riley Myers (Application team lead), Andrea George, Vicky Borders-Hemphill, Amy Devlin, Thuy Thanh Nguyen, Michael Shanks, Candace Gomez-Broughton, Joanna Zhou, Shamika Brooks	May 29, 2020
Clinical	Dolly Misra	June 12, 2020
Statistics	Anna Kettermann	April 15, 2020; amended June 13, 2020
Clinical Pharmacology		
Nonclinical	Dan Minck	May 5, 2020
CDRH	David Wolloscheck	April 16, 2020
DMEPA	Ariane Conrad, Janine Purcell; Carlos Mena-Grillasca	May 7, 2020 (Human Factors review); June 5, 2020 (Labeling review); February 7, 2020 (proprietary name review); February 6, 2020 (nonproprietary name suffix)
OPDP	Ankur Kalola	May 19, 2020
Patient Labeling	Nyedra Booker, Ankur Kalola	May 21, 2020
Clinical Inspections (OSI)	Cynthia Kleppinger	April 8, 2020
PeRC Minutes	PeRC	April 28, 2020
DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion; OSI: Office of Scientific Investigations; PeRC: Pediatric Review Committee; CDRH: Center for Devices and Radiologic Health		

2. Background

Insulin lispro-aabc is a 51 amino acid, two-chain peptide, human insulin analog. The A-chain has 21 amino acids and the B-chain has 30. Insulin lispro-aabc differs from regular human insulin at the C-terminal end of the B-chain, where amino acids lysine and proline are reversed. The modification prevents formation of insulin dimers and hexamers, leading to more rapid absorption compared to regular human insulin, when administered by subcutaneous injection. Insulins, including insulin lispro-aabc, bind insulin receptors and lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat and by inhibiting hepatic glucose production, lipolysis, and proteolysis. Humalog (insulin lispro) was approved for use in the United States in June 1996, manufactured and marketed Eli Lilly and Company (as new drug application [NDA] 20563). Humalog Mix 75/25 (insulin lispro and insulin lispro protamine) and Humalog Mix 50/50 (insulin lispro and insulin lispro protamine) were approved in the US in 1999 (as NDA 21017 and NDA 21018, respectively). The Humalog insulin lispro products have been approved to improve glycemic control in adults and children with diabetes mellitus.

Eli Lilly and Company (hereafter the Applicant) submitted its 351(a) application for Lyumjev (also known as LY900014), on August 15, 2019. Lyumjev/LY900014 is formulated with insulin lispro-aabc and also incorporates (b) (4) treprostinil (b) (4) and citrate (b) (4) I will primarily refer to the product as LY900014 throughout the rest of the summary memo, to maintain consistency with the underlying review.

Based on the results of its development program, the Applicant has proposed the following indication for LY900014: to improve glycemic control in adults with diabetes mellitus. The Applicant has also proposed the results of its development program support dosing LY900014 by subcutaneous inject (b) (4) within 20 minutes of starting a meal. The Applicant has also proposed that LY900014 can be dosed intravenously. The Applicant proposes to make LY900014 available in 2 dosage strengths (100 units/ml or "U-100" and 200 units/ml or "U-200"). The U-100 preparation has several proposed presentations (10 ml vial, 3 ml cartridge, and three different prefilled pen options); the U-200 preparation has one proposed presentation (a prefilled pen). The Applicant proposes to study the use of LY900014 in pediatric patients and in continuous subcutaneous infusion pumps after approval.

3. CMC/Device

The insulin lispro-aabc drug substance is produced in genetically engineered *Escherichia coli*. The LY900014 drug product (DP) is formulated from the DS and has the following presentations for subcutaneous injection and/or intravenous infusion:

U-100:

- 10 ml multiple-dose vial

- 3 ml single-patient-use KwikPen
- 3 ml single-patient-use Junior KwikPen
- 3 ml single-patient-use Tempo Pen
- 3 ml single-patient-use cartridge

U-200:

- 3 ml single-patient-use KwikPen

The OBP Quality Review Team concluded that the data submitted in the application support the conclusion that the manufacture of insulin lispro-aabc (LY900014) is well-controlled and leads to a product that is pure and potent and recommends approval of STN 761109 for insulin lispro-aabc. Andrea George reviewed the Drug Substance, Drug Product, and immunogencity data. Vicky Borders-Hemphill reviewed the labeling. Amy Devlin and Michael Shanks reviewed the Drug Substance microbiology and the facility. Riley Myers served as the Application Team Lead. Please see the OBP Multidisciplinary Review for details regarding the Quality Assessments. I concur with their conclusions.

Drug Substance

Insulin lispro-aabc DS fermentation is performed at Lilly del Caribe in Carolina, Puerto Rico (FEI 3004525072). Insulin lispro DS-aabc purification is performed at Lilly del Caribe in Carolina, Puerto Rico (FEI 3004525072) and Eli Lilly and Co in Indianapolis, IN, USA (FEI 1819470).

Drug Product

Final drug product is produced at Eli Lilly and Company Lilly Corporate Center Indianapolis, IN, USA [manufacture of cartridge and vial drug product, primary and secondary packaging, assembly of pre-filled pen injectors, release testing (vial only), in-process testing, stability testing, raw material testing and approval] and at Lilly France 2, rue du Colonel Lilly 67640, Ferfersheim France (FEI 3002807475) [secondary drug product packaging (cartridge only), assembly and testing of pre-filled pen injector, drug product release and stability testing). LY900014 is formulated in 4.41 mg sodium citrate dihydrate, 1.02 magnesium chloride hexahydrate, 12.1 mg glycerol, and 3.15 mg metacresol in water for injection (WFI) with 1.06 micrograms treprostinil and zinc oxide to provide a final zinc concentration of 39 micrograms for 100 U/mL or 52 micrograms for 200 U/mL. All the excipients except for treprostinil are compendial.

Facilities

OPQ relied on a FDCA 704(a)(4) review of requested inspection documents. The most recent inspection (ORA), facility history, District File Review, and FDAC 704(a)(4) for the DS manufacturing sites FEI 3004525072 and FEI 1819470 and DP manufacturing site FEI 1819470 were all found adequate. Therefore, OMPQ on-site PLI was waived for those sites. A Part 4 Medical Device QSIT inspection from 1/13/2020 to 1/16/2020 was performed with no FDA Form 483 issued for LY900014 for DP manufacturing site FEI 3002807475; a District

File Review was approved based on the inspection. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage.

Device/CDRH

David Wolloscheck from CDRH conducted the device review. CDRH has previously reviewed the Applicant's KwikPens under the Humalog NDA (now BLA). The device component of the LY900014 combination biologic-device products is the same in terms of the mechanics as in the Humalog combination biologic-device products. Accordingly, the Application leveraged the majority of the data from the previously approved KwikPens. While the Applicant has included the 100 U/mL Tempo Pen and while the Applicant has had meetings with CDRH to discuss how the Tempo Pen may be used with an external data transfer module, the Applicant clarified that the intended use and indications for the Tempo Pen are identical to the 100 U/mL Kwik Pen – that is, as a stand-alone device, the Tempo pen may be used in a fungible manner with the KwikPen. Dr. Wolloscheck concluded that the device constituent for all the combination products are approvable for the proposed indications. I concur with his conclusion. For additional details, please see Dr. Wolloscheck's review.

4. Nonclinical Pharmacology/Toxicology

Daniel Minck of the Division of Pharmacology Toxicology for Cardiology, Hematology, Endocrinology and Nephrology conducted the nonclinical review. Given previously evaluated studies conducted and submitted by the Applicant to the Humalog NDA (now BLA) in 1996, the nonclinical review of the submission comprised an assessment of the excipient treprostinil (the only non-compendial excipient in LY900014). Dr. Minck concluded that BLA 761109 is approvable from the Pharmacology/Toxicology perspective, and I concur.

Treprostinil, a prostacyclin analog with vasodilatory activity, is the active ingredient of several products (Remodulin, Orenitram, and Tyvaso) approved for the treatment of pulmonary arterial hypertension (PAH). The Applicant conducted their own nonclinical studies to support the use of treprostinil in LY900014. However, it is worth noting that the dose of treprostinil in LY900014 is around 15 mg/kg/day, which is well below the starting dose of Remodulin (1800 mg/kd/day).

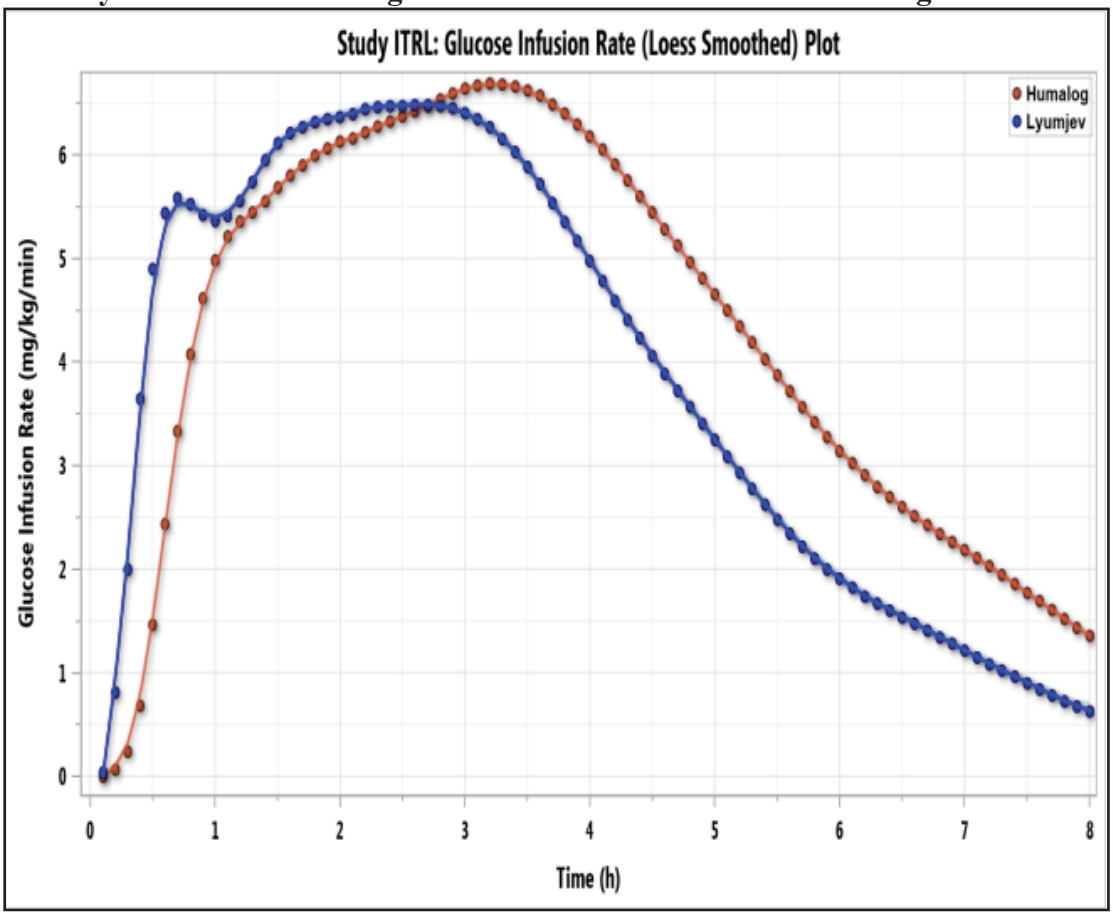
Pharmacology studies were conducted with LY900014 while safety pharmacology, pharmacokinetic, and toxicology studies were conducted with treprostinil alone. The studies showed no effects on respiratory or central nervous system functioning. Prolonged QT/QTc times were observed in dogs, but only at multiples greater than 50-fold the clinical exposure to treprostinil associated with LY900014. In rat and dog models, transient red discoloration of the skin of test species was observed. Genotoxicity studies did not reveal evidence of mutagenicity and reproductive toxicology studies did not reveal evidence of effects on fertility or pre-natal or post-natal development. Increased post-implantation loss was observed in rabbits, but only an exposure many thousand-fold above the expected clinical exposure associated with use of LY900014.

5. Clinical Pharmacology/Biopharmaceutics

Suryanarayana Sista, Liang Li, Justin Earp, and Manoj Khurana of the Office of Clinical Pharmacology (OCP) conducted the clinical pharmacology and pharmacometric review of the BLA submission. The review considered data from three pharmacodynamic studies; one absorption, metabolism, and elimination study; one QTc study. In addition, clinical pharmacology data were collected for 6 of the 9 Phase 3 studies of LY900014.

A euglycemic clamp studies comparing the PK/PD profiles of LY900014 and Humalog were conducted in healthy volunteers (Study ITRL). Study ITRL was a Phase 1, single center, randomized, double-blind, 2-treatment, 2-period, crossover study. The Clinical Pharmacology Review concluded based on the data generated that LY900014 exhibited a slightly larger insulin onset of action within the first after administration compared to Humalog, similar exposures, and shorter duration of action (see Figure 1 and Table 1). The FDA clinical pharmacology review also leveraged Study ITRL to compare the PK profiles of LY900014 and Humalog (see Figure 2 and Table 2). Other studies yielded similar PK and PD data in the T1D and T2D patient populations.

Figure 1: Mean Locally Weighted Scatterplot Smoothing Fits of Glucose Infusion Rate vs Time by Treatment following 15 U doses of LY900014 and Humalog



Source: FDA Clinical Pharmacology Review of BLA 761109

Table 1: Pharmacodynamic parameters and statistical analysis after administration of 15 U of LY900014 or 15 U of Humalog

Parameter	Treatment	N	Geometric Least squares means	Ratio of geometric least squares means Test : Reference	90% CI for the ratio (Lower, Upper)	P-value
Rmax (mg/min)	15 U Humalog	32	460.14			
	15 U LY900014	32	462.89	1.01	(0.94, 1.08)	0.887
Gtot (mg)	15 U Humalog	32	125414.28			
	15 U LY900014	32	115047.58	0.92	(0.85, 0.99)	0.072

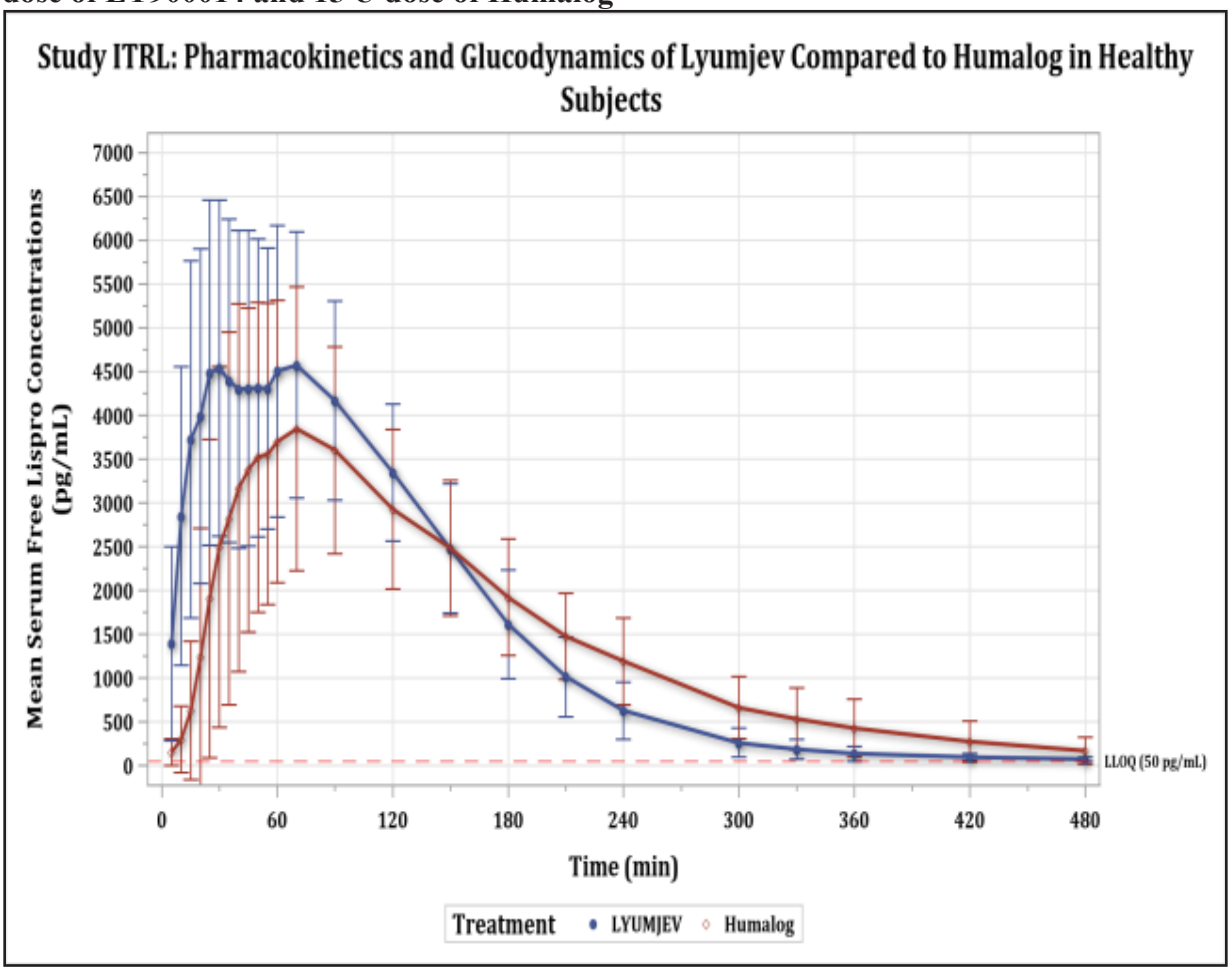
Parameter	Treatment	N	LS means	Difference in LS means (Test - Reference)	90% CI for the difference (Lower, Upper)	P-value	Ratio of LS means (Test : Reference)	90% CI for the ratio (Lower, Upper)
Tonset (min)	15 U Humalog	32	33.97					
	15 U LY900014	32	20.10	-13.88	(-15.85,-11.90)	<.0001	0.59	(0.55,0.63)
tRmax (min)	15 U Humalog	32	170.81					
	15 U LY900014	32	131.25	-39.56	(-62.70,-16.43)	0.0069	0.77	(0.66,0.90)
early 50% tmax (min)	15 U Humalog	32	55.07					
	15 U LY900014	32	29.33	-25.75	(-33.20,-18.29)	<.0001	0.53	(0.45,0.63)
late 50% tmax (min)	15 U Humalog	31	335.84					
	15 U LY900014	32	273.67	-62.18	(-77.73,-46.62)	<.0001	0.81	(0.76,0.87)

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

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

Source: FDA Clinical Pharmacology Review of BLA 761109

Figure 2: Mean Insulin Lispro Concentration Versus time by Treatment following 15 U dose of LY900014 and 15 U dose of Humalog



Source: FDA Clinical Pharmacology Review of BLA 761109

Table 2: Summary of Clinical Pharmacokinetics of LY900014

Absorption:	• Following administration of LYUMJEV, insulin lispro appeared in the circulation within 1 min after injection following a 15 U dose. The early 50% T_{max} (time to 50% maximum insulin lispro concentration) for insulin lispro from LYUMJEV following SC administration is approximately 13 minutes. • Insulin lispro exposure with LYUMJEV was similar regardless of injection site. • The overall insulin lispro exposure and time of maximum observed drug concentration (T_{max}) was comparable between LYUMJEV and Humalog. From the PK meta-analysis, the median time to maximum insulin lispro (T_{max}) was approximately 1 hour (range 0.17 to 3 hours) after SC administration of LYUMJEV. • The amount of insulin lispro that reached the circulation relative to an IV dose (absolute bioavailability) after SC administration of LYUMJEV into the abdomen, deltoid and thigh was approximately 65% in healthy subjects.
Distribution:	• Following IV injection of a 15 U dose of LYUMJEV, the mean (range) volume of distribution (Vz) was 34 L (16 - 53 L).
Elimination:	• Mean (range) clearance of insulin lispro following IV injection of a 15 U dose of LYUMJEV was 32.3 L/h (23.3 - 49.5 L/h), with a mean elimination half-life of 0.73 h (0.47 - 1.23 h) • Mean clearance (CL/F) of insulin lispro following SC injection of a 15 U dose of LYUMJEV was 51 L/h (40 – 88 L/h), with a mean half-life of 0.70 h (0.46 – 1.00 h).
Metabolism:	• Human metabolism studies were not conducted for LYUMJEV, since the peptide LYUMJEV is expected to undergo degradation to small peptides and individual amino acids.

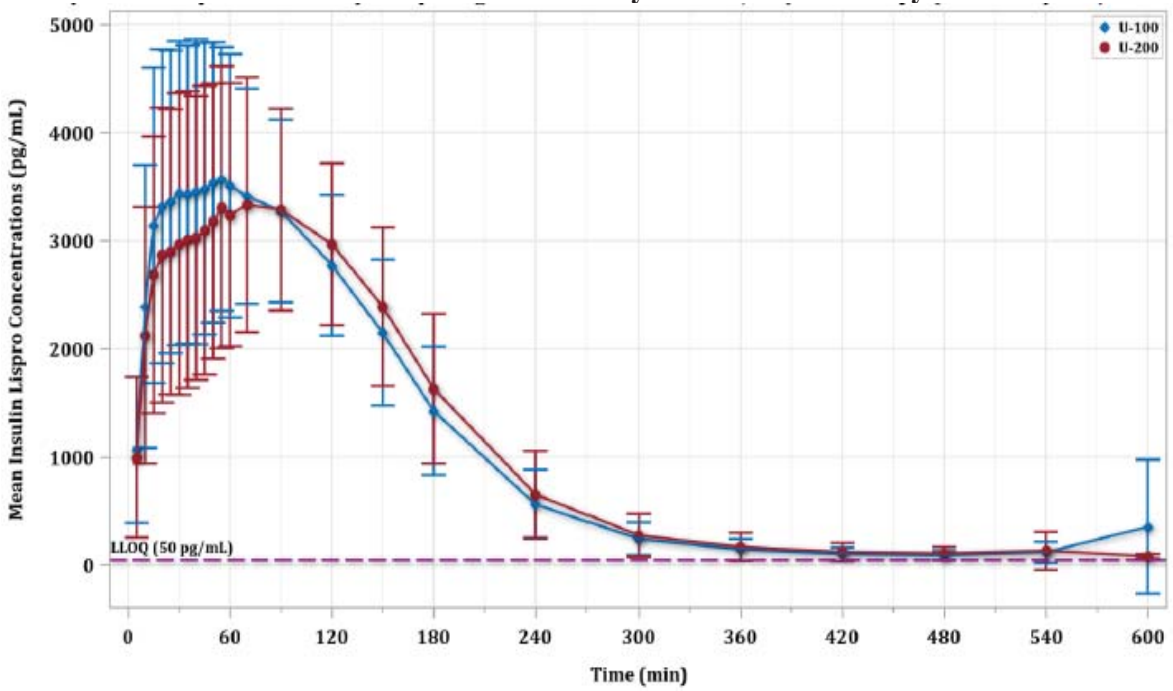
Source: FDA Clinical Pharmacology Review of BLA 761109

As discussed at the End-of-Phase 2 meeting, the Applicant conducted and submitted a bioequivalence (BE) study (ITSS) to support the approval of the U-200 presentation of LY-900014. The BLA submission also included data and analyses to support the rationale provided by the Application to label postmeal dosing of LY900014 in patients with type 2 diabetes (T2D) based on the data generated in the postmeal dosing arm of the pivotal phase 3 study in type 1 diabetes (ITRM), the data generated in two meal challenge PK/PD studies (ITRV in patients with T1D and ITRQ in patients with T2D), and on the results of pharmacometric modeling. The FDA clinical pharmacology team concluded that the data support the approval of the BLA, including the approval of the U-200 strength and the postmeal dosing of LY900014 in the T2D patient population. I concur with their conclusions.

ITSS

Study ITSS was a Phase 1, single-center, subject- and investigator-blind, randomized, 2-sequence, 4-period, crossover, 10-hour euglycemic clamp study in 68 healthy subjects. The study compared the pharmacokinetics (PK) and pharmacodynamics (PD) of LY900014 U-100 and U-200 formulations following a single 15-unit subcutaneous dose. The mean insulin lispro concentrations following administration of the LY900014 U-100 and U-200 doses are shown in Figure 3.

Figure 3: Mean Insulin Lispro Concentrations Versus Time Following Single 15 U SC Dose on LY900014 U-200 and U-100 in Healthy Volunteers in Study ITSS



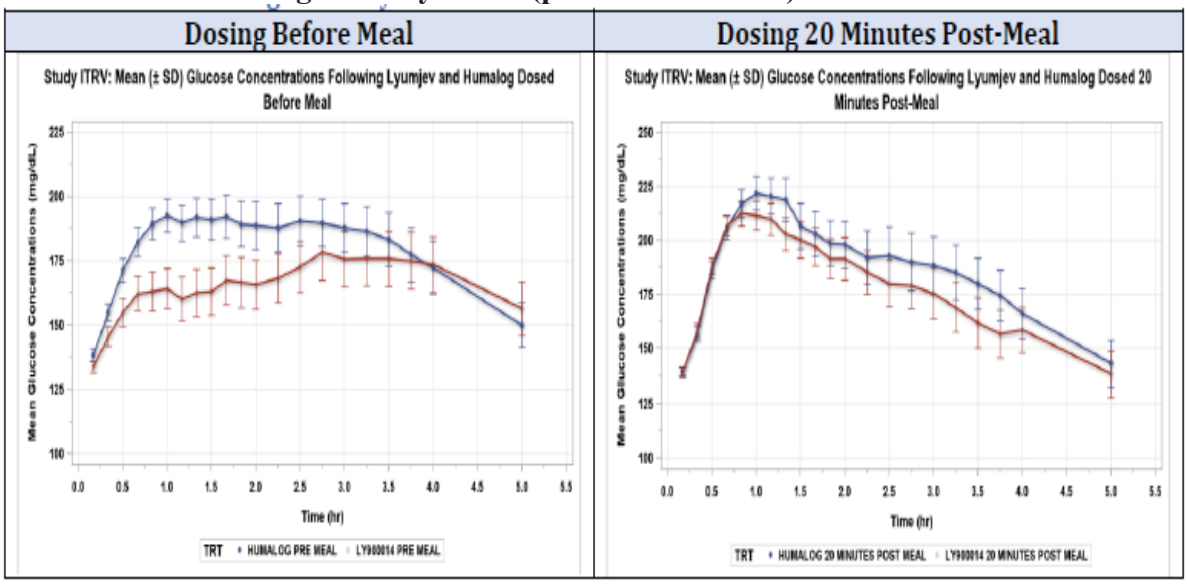
Source: FDA Clinical Pharmacology Review of BLA 761109

A comparison of the primary PK parameters showed that the ratio of U-200/U-100 were 1.01 for $AUC_{(0\text{-}10h)}$, $AUC_{(0\text{-}tlast)}$, and $AUC_{(0\text{-}infinity)}$ and 0.97 for C_{max}. The 90% CIs for all the ratios were contained in the BE limits (0.8, 1.25), demonstrating the bioequivalence of the two formulations.

ITRV and ITRW

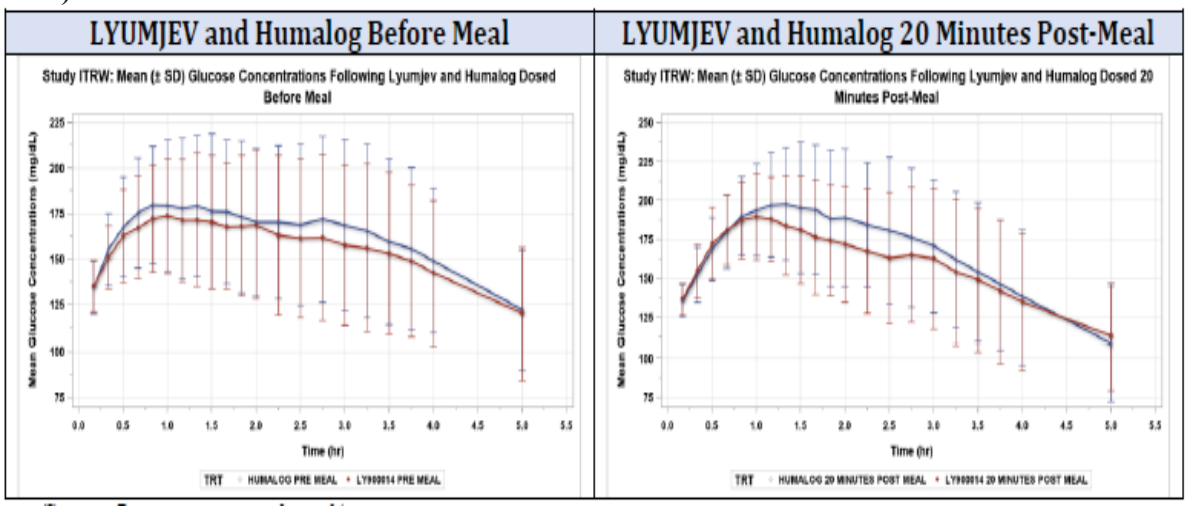
Study ITRV was a Phase 1, randomized, patient- and investigator-blind, 2-treatment, 4-period crossover study in patients with T1D to evaluate PK following a single SC injection of LY900014 and Humalog. The study also compared the PD profiles of LY900014 and Humalog immediately before and 20 minutes after the start of the meal (see Figure 4). Study ITRW was an identical study in patients with T2D (see Figure 5).

Figure 4: Mean glucose concentration versus time post meal dosed immediately before (left) and 20 minutes after the start of a test meal (right) following a single sc dose LY900014 or Humalog in Study ITRV (patients with T1D)



Source: FDA Clinical Pharmacology Review of BLA 761109

Figure 5: Mean glucose concentration following individualized doses of LY900014 or Humalog before meals (left) or 20 minutes postmeal (right) in Study ITRW (patients with T2D)



Source: FDA Clinical Pharmacology Review of BLA 761109

The Clinical Pharmacology review concluded that Study ITRV showed that LY900014 exhibited a greater reduction in change from baseline postprandial glucose (PPG) excursion up to 4 hours postmeal in patients with T1D compared to Humalog. The difference between LY900014 and Humalog was not statistically significant when both were dosed 20 minutes after the start of the meal. The reduction in change in baseline PPG excursion over the 5-hour mean tolerance test (MMTT) was similar between LY900014 and Humalog when LY900014

was dosed 20 minutes after the start of the meal and Humalog was dosed immediately before the start of the meal.

The Clinical Pharmacology review concluded that Study ITRW showed a numerically (but not statistically significant) greater reduction in baseline PPG excursion up to 4 hours postmeal with LY900014 in patients with T2D compared to Humalog. The difference between LY900014 and Humalog was not statistically significant when both were dosed 20 minutes after the start of the meal. Similarly, the postprandial glucose excursion over the 5-hour MMTT was statistically not significantly different between LYUMJEV and Humalog when LYUMJEV was dosed 20 minutes after the start of the meal and Humalog was dosed immediately before the start of the meal.

Pharmacometrics Assessment

The Applicant conducted E-R analyses separately for T1D and T2D to quantify the relationship between drug concentration and postprandial glucose response following SC administration of LYUMJEV and Humalog when both insulins are given prior to the start of the meal and 20 minutes after the start of the meal. The pharmacometrics reviewer concluded that the Applicant's model simulations demonstrated a similar PPG excursion for when LYUMJEV is dosed 20 minutes post meal to when Humalog is dosed immediately before the start of the meal.

Overall, the FDA clinical pharmacology review concluded that the data from the pivotal Phase 3 studies (see section 6) and Studies ITRV and ITRW, in conjunction with the pharmacometrics assessment, support the proposed administration of LYUMJEV within 20 minutes after starting a meal in patients with T1D and in patients with T2D from the efficacy perspective.

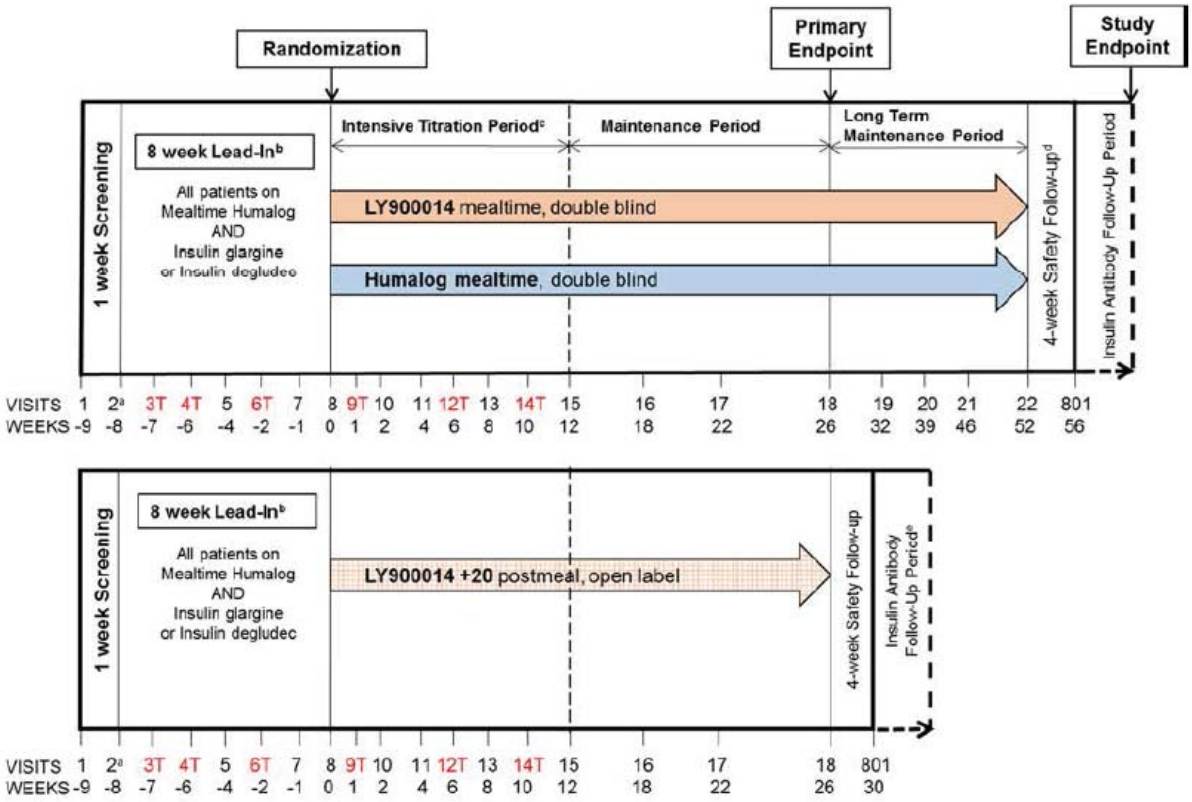
6. Clinical/Statistical- Efficacy

Dolly Misra (from the Division of Diabetes, Lipid Disorders, and Obesity) and Anna Kettermann (from the Office of Biostatistics) reviewed the clinical/statistical data submitted in support of LY900014. The clinical development program for LY9000014 included 18 clinical pharmacology studies and 3 phase 3 trials [including two multiple daily injection (MDI) studies and one continuous subcutaneous insulin infusion study (CSII)]. The two MDI trials were ITRM (also known as PRONTO-T1D) and ITRN (also known as PRONTO-T2D). Data from the CSII trial (ITSI) were included in the BLA submission, but the Applicant is not currently seeking an indication for CSII administration. For that reasons, Drs. Misra and Kettermann focused their assessment of efficacy on the two pivotal Phase 3 MDI studies. Drs. Misra and Kettermann determined that the data support the conclusion that LY900014 is non-inferior to Humalog as measured by change from baseline to Week 26 in HbA1c. Dr. Misra also concluded that (together with the data from the clinical pharmacology studies and the results of the pharmacometric models) that LY900014 may be dosed at mealtime or up to 20 minutes after the start of a meal. I concur with the conclusions of Drs. Misra and Kettermann. See the reviews of Drs Misra and Kettermann for additional details.

ITRM

Study ITRM (PRONTO-T1D) was a 52 week, prospective, randomized, double-blind comparison of LY900014 to Humalog, in combination with insulin glargine or insulin degludec, in adults with T1D. The primary objective of this study was to demonstrate that LY900014 was 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 in combination with basal insulin glargine or insulin degludec in patients with T1D. In 2 of the treatment groups, LY900014 and Humalog were administered immediately (0-2 minutes) prior to the start of the meal in a double-blind manner. A third open-label treatment group consisted of LY900014 administered 20 minutes after the start of a meal (LY+20). See Dr. Misra's clinical review for details including inclusion/exclusion criteria, randomization strategy, titration of basal and prandial insulin doses, and secondary efficacy endpoints.

Figure 6: Study Design ITRM



Source: ITRM Clinical Study Report

Of the 1621 patients screened for Study ITRM, 1222 patients were randomized (Humalog =442; LY900014 =451; LY+20 =329). **T**reatment discontinuation rates were low, with over 94% of patients completing 26 weeks of treatment. The demographics of the study population revealed the mean age of patients was 44.36 years. and the majority of patients (92.0 %) were under 65 years of age. More than half of the patients were male (56.3%) and the majority of patients were White (77.3%), followed by Asian (18.6%) and Black/African American (1.7%).

In this multinational trial, the US comprised the greatest number of patients (29.3%), followed by Japan (13.7%). The baseline disease characteristics for the diabetic study participants revealed the mean duration of diabetes was 18.9 years. Patients had a mean BMI of 26.55 kg/m^2 and mean weight of 77.37 kg at baseline. The mean HbA1c at screening was 8.03%, and at the end of the lead-in period, during which basal insulin was optimized, the mean HbA1c was 7.34%. Insulin therapy used prior to study participation included basal insulin treatment with insulin glargine (57.8%), insulin degludec (30.9%), insulin detemir (8.9%), and NPH (2.4%). Pre-study bolus insulin treatment included insulin aspart (48.9%), insulin lispro (38.4%) and insulin glulisine (12.8%). The prandial insulin dosing plan was pattern adjustment in 54.7% of patients and carbohydrate counting in 45.3%.

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment (see **Table 3** for results).

Mealtime LY900014 vs Humalog change in HbA1c for non-inferiority: In the FDA analysis, the change from baseline in HbA1c after 26 weeks of treatment was -0.12% with mealtime LY900014 compared to -0.04% with Humalog. The treatment difference of -0.08 with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: -0.16, 0.00) established non-inferiority. The upper limit of the 95% CI for the difference in change in HbA1c was also less than the noninferiority margin of 0.3%.

Mealtime LY900014 vs Humalog change in HbA1c for superiority: LY900014 was found to be statistically superior to Humalog; the 95% CI for difference between LY900014 and Humalog was below zero.

LY+20 vs Humalog change in HbA1c for non-inferiority: In the FDA analysis, the change from baseline in HbA1c after 26 weeks of treatment was 0.01% with LY+20 compared to -0.04% with Humalog. The treatment difference of 0.14 with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: 0.05, 0.22) established noninferiority. The upper limit of the 95% CI for the difference in change in HbA1c was also less than the noninferiority margin of 0.3%.

Table 3: Primary Analysis Outcomes Study ITRM

Treatment	LY900014 N = 451	LY900014+20 N=329	Humalog N = 442
Baseline HbA1c (%) Mean (std)	7.3 (0.65)	7.4 (0.64)	7.3 (0.67)
Adjusted Mean Change from Baseline	-0.12	0.10	-0.04
Difference between treatment and Humalog (95% CI)	-0.08 (-0.16, 0.00)	0.14 (0.05, 0.22)	

Source: Data from BLA 761109 as analyzed by FDA statistical reviewer in support of labeling

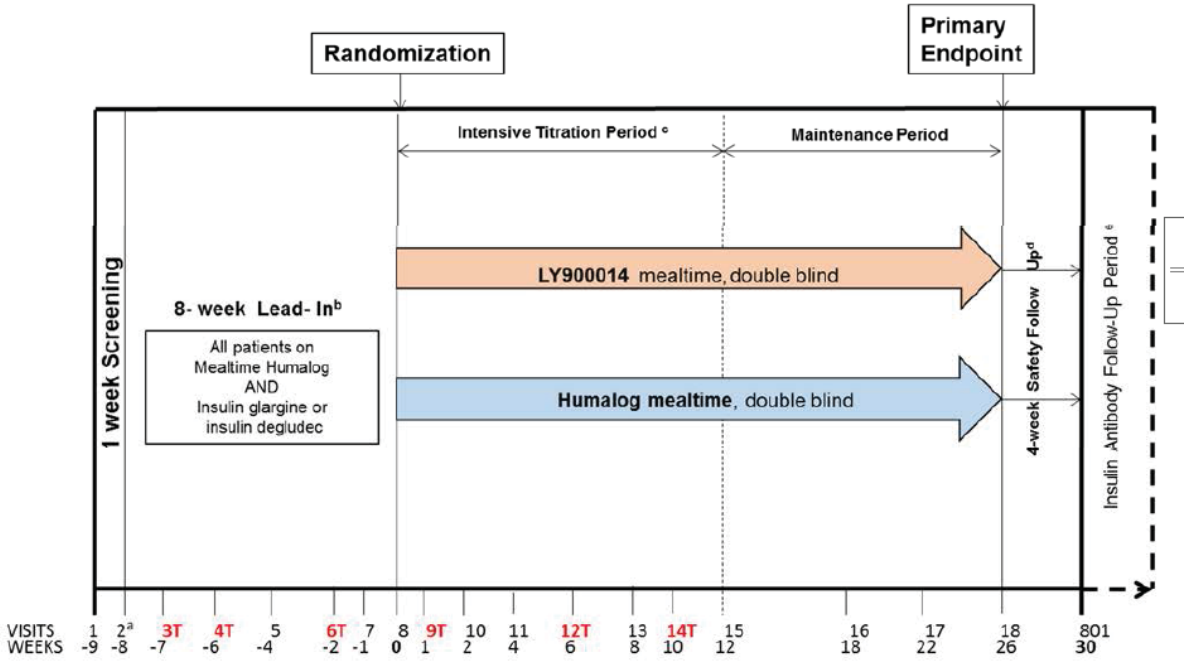
CDTL comment: From a statistical perspective, mealtime LY900014 narrowly demonstrated superiority to Humalog with regard to the primary endpoint – the difference between mealtime

LY900014 and Humalog was -0.08 with an upper bound of the CI of zero. Clinically, however, the small difference observed between the two treatments is not significant. Moreover, while the doses of basal insulin were similar across treatment arms, they were not identical (the mean doses were slightly higher among patients treated with LY900014). In addition, the finding of statistical superiority was not replicated in the Phase 3 trial in patients with T2D (ITRN, see below). Therefore, the FDA statistical reviewer, the FDA primary clinical reviewer, and I all agree that superiority was not demonstrated. However, efficacy was demonstrated on the basis of meeting the pre-specified non-inferiority margin for both mealtime LY900014 and postmeal LY900014 compared to mealtime Humalog.

ITRN

Study ITRN (PRONTO-T2D) was a 26-week prospective, randomized, double-blind comparison of LY900014 to Humalog, both in combination with insulin glargine or insulin degludec in adults with T2D. The primary objective of this study was to demonstrate that LY900014 was 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 prandial insulin in combination with basal insulin glargine or insulin degludec in patients with T2D. The study had 2 double-blind groups to allow comparison of LY900014 and Humalog when injected at the start of the meal. See Dr. Misra's clinical review for details including inclusion/exclusion criteria, randomization strategy, titration of basal and prandial insulin doses, and secondary efficacy endpoints.

Figure 7: Study Design ITRN



Source: ITRN Clinical Study Report

Of 963 patients screened, 673 were randomized (Humalog =337; LY900014 =336). Treatment discontinuation rates were low with over 95% of patients completing 26 weeks of treatment

(Humalog=319 patients; LY900014=320 patients). The mean age of the study population was 60 years, with 60% of patients under 65 years of age and 97% under 75 years. More than half of the patients were male (53.3%) and the majority of patients were White (68.6%), followed by Asian (24.4%) and Black/African American (4.5%). The US comprised the 27% of study participants. The baseline disease characteristics for study participants revealed the mean duration of diabetes was 16.5 years. Patients had a mean BMI of 32.28 kg/m^2. The mean HbA1c at screening was 8.3% and 7.3% following basal insulin titration, prior to randomization. Prestudy basal insulin treatment showed use of insulin glargine (65.7%), insulin detemir (12.0%), NPH (11.3%), and insulin degludec (11.1%). Oral antidiabetic medication used by patients prior to study participation included metformin (70.6%) and SGLT-2 inhibitor (17.7%).

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment (see **Table 4**). In Study ITRN, dosing with LY900014 20 minutes after meal was not studied.

Table 4: Primary Analysis Study ITRN

Treatment	LY900014 N = 336	Humalog N = 337
Baseline HbA1c (%) Mean (std)	7.3(0.68)	7.3(0.72)
Change in HbA1c	-0.36	-0.38
Difference between treatment and Humalog (95% CI)	0.03 (-0.08, 0.13)	

Source: Data from BLA 761109 as analyzed by FDA statistical reviewer in support of labeling

LY900014 vs Humalog change in HbA1c for non-inferiority: In the FDA analysis, the change from baseline in HbA1c after 26 weeks of treatment was -0.36% with LY900014 compared to -0.38% with Humalog. The treatment difference of 0.03 with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: -0.08, 0.13) established non-inferiority. The upper limit of the 95% CI for the difference in change in HbA1c was also less than the noninferiority margin of 0.3%.

LY900014 vs Humalog change in HbA1c for superiority: LY900014 was not found to be superior to Humalog, as the treatment difference and 95% CI for the difference between LY900014 and Humalog was not below zero.

CDTL Comment: the FDA statistical reviewer, the FDA primary clinical reviewer, and I all agree that efficacy was demonstrated on the basis of meeting the pre-specified non-inferiority margin for mealtime LY900014 compared to mealtime Humalog.

CDRL Comment: At the pre-BLA meeting, the Applicant proposed that the totality of data from the Phase 3 studies, clinical pharmacology mealtime studies (ITRV and ITRW) and the model-based simulations, support the dosing of LY90014 at the start of the meal and 20 minutes after the start of the meal in patients with T2D as well as T1D. FDA agreed that this data package appeared adequate to support review of a post-meal dosing indication in patients with T1D and T2D. As previously described, postmeal LY900014 administration was demonstrated to be noninferior to Humalog on glycemic control in the pivotal Study ITRM in patients with T1D. The Applicant's clinical pharmacology studies comparing postmeal dosing of LY900014 to mealtime Humalog in patients with T1D and T2D for PPG excursion following MMTT showed that the PPG excursion over the 5-hour MMTT was not statistically significantly different between LY900014 and Humalog when LY900014 was dosed 20 minutes after the start of the meal and Humalog was dosed immediately before the start of the meal. Additionally, the simulations from the pharmacometrics assessment suggest that the safety of postmeal dosing of LY900014 in patients with T2D, with respect to hypoglycemia, is comparable to that of Humalog (see section 5). In addition, as detailed in her review, Dr Misra's clinical judgment is that adverse safety or efficacy findings associated with insulin products such as LY900014 are more likely be captured in trials with T1D patients than with T2D patients, as the T2D population is less insulin sensitive. Overall, she therefore concluded the data support postmeal dosing in the T2D population as well as the T1D population. I concur with her assessment.

7. Safety

Dolly Misra (from the Division of Diabetes, Lipid Disorders, and Obesity) also reviewed the clinical safety data supporting BLA 761109. She based her assessment of safety primarily on the data from the pivotal MDI trials (ITRM and ITRN). She also considered supported safety data from the CSII trial (ITSI). She concluded, and I concur, that the safety data support a finding of a favorable benefit-risk profile for LY900014. See Dr. Misra's clinical review for additional details.

In summary, the safety data from ITRM and ITRN were generally integrated. However, certain safety outcomes were assessed individually due the differences in dosing regimens (i.e., the inclusion of a postmeal dosing arm in ITRM): dropouts, treatment discontinuations, deaths, and hypoglycemia. No notable differences across dosing regimens or study populations were observed for these safety parameters.

The review of the safety data from ITSI was not integrated with the MDI trials because of the differences in route of administration and differences in study design (e.g., study duration): during the treatment periods, there were no deaths or discontinuations due to AEs. The incidence of patients reporting at least 1 TEAE was higher among patients receiving LY900014 (46.9%) than patients receiving Humalog (18.8%); this difference was driven by infusion site reactions.

Exposure in Phase 3 MDI trials

Details about the safety population and duration of exposure to study drug administered in trials ITRM and ITRN is presented in Table 5).

Table 5: Summary of Exposure to Investigational Product from Randomization to Week 52 in ITRM and ITRN

	Study ITRM (T1D)		Study ITRN (T2D)		Total	
	Humalog (N=442)	All LY (N=780)	Humalog (N=337)	All LY (N=336)	Humalog (N=779)	All LY (N=1116)
Days of exposure, n (%)						
>0 to <30 days	1 (0.2)	4 (0.5)	1 (0.3)	5 (1.5)	2 (0.3)	9 (0.8)
≥30 to <90 days	11 (2.5)	16 (2.1)	8 (2.4)	5 (1.5)	19 (2.4)	21 (1.9)
≥90 to <180 days	9 (2.0)	47 (6.0)	33 (9.8)	45 (13.4)	42 (5.4)	92 (8.2)
≥180 to <360 days	84 (19.0)	327 (41.9)	295 (87.5)	281 (83.6)	379 (48.7)	608 (54.5)
>360 days	337 (76.2)	386 (49.5)	0	0	337 (43.3)	386 (34.6)

Abbreviations: All LY = LY900014 administered 0 to 2 minutes prior to the start of the meal or administered 20 minutes after the start of a meal; N = number of patients in the analysis population; n = number of patients in the specified category; T1D = type 1 diabetes; T2D = type 2 diabetes. **Source: Table 2.7.4.3 Summary of Clinical Safety**

Results

In the MDI studies, six deaths were observed (4 among patients treated with LY900014 and 2 among patients treated with Humalog) prior to database lock. An additional 4 deaths were reported after the safety follow-up visit (three among patients treated with LY900014 and 1 among patients treated with Humalog). Dr. Misra reviewed the narratives for all the deaths and concluded that they were unlikely to have been causally associated with the investigational products.

In general, adverse events and serious adverse events were consistent with the known adverse reactions associated with insulin products and similar across treatment arms (see Table 6 and Table 7). Treatment discontinuations due to adverse events were generally similar across treatment arms in the MDI studies: 1.7% of patients receiving LY900014 discontinued due to adverse events, compared to 1.0% of patients receiving Humalog (see Table 8).

Table 6: Adverse Events in Safety Populations of ITRM and ITRN

Number of Subjects*a	Humalog (N=779) n (%)	All LY (N=1116) n (%)	Total (N=1895) n (%)	OR*d	Heterogeneity P-value*e	P-value*f
Deaths*b	2 (0.3)	4 (0.4)	6 (0.3)	1.52	0.740	0.624
Serious Adverse Events	100 (12.8)	113 (10.1)	213 (11.2)	0.73	0.342	0.030
Discontinuations from Study due to an Adverse Event	4 (0.5)	10 (0.9)	14 (0.7)	1.78	0.819	0.333
Discontinuations from Study Treatment due to an Adverse Event	8 (1.0)	18 (1.6)	26 (1.4)	1.58	0.658	0.282
Treatment-emergent Adverse Events	493 (63.3)	704 (63.1)	1197 (63.2)	0.96	0.134	0.675
Treatment-emergent Adverse Events Related to Study Treatment*c	49 (6.3)	79 (7.1)	128 (6.8)	1.03	0.410	0.863

Abbreviations: All LY = LY900014 administered 0-2 minutes prior to the start of the meal or administered 20 minutes after the start of a meal; N = number of subjects in the analysis population; n = number of subjects with at least one adverse event per event type.
*a - Subjects may be counted in more than one category.
*b - Deaths are also included as serious adverse events and discontinuations due to adverse events.
*c - Includes events that were considered related to study treatment as judged by the investigator.
*d – Mantel-Haenszel Odds Ratio stratified by study. All LY is numerator
ty of odds ratios across studies was assessed using the Breslow Day test
p-values are from Cochran-Mantel-Haenszel (CMH) test of general association stratified by study. MedDRA Version 21.1 **Source: Summary of Clinical Safety Table 2.7.4.9**

Table 7: Serious Adverse Events by Preferred Term Reported by >1 Patient from Randomization to Safety Follow-Up in ITRM and ITRN

	Humalog (N=779)	All LY (N=1116)	Total (N=1895		Heterogeneity	
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**OR[a]**	**p-**	**p-value[c]**
Patients with ≥1 SAE	100 (12.8)	113 (10.1)	213 (11.2)	0.73	0.342	0.030
Hypoglycaemia	45 (5.8)	53 (4.7)	98 (5.2)	0.69	0.952	0.077
Pneumonia	2 (0.3)	5 (0.4)	7 (0.4)	2.09	0.247	0.347
Cellulitis	1 (0.1)	3 (0.3)	4 (0.2)	1.92	0.399	0.546
Angina pectoris	0 (0.0)	3 (0.3)	3 (0.2)	NC	NC	0.147
Chronic obstructive pulmonary disease	0 (0.0)	3 (0.3)	3 (0.2)	NC	NC	0.082
Nephrolithiasis	0 (0.0)	3 (0.3)	3 (0.2)	NC	NC	0.111
Gastroenteritis	1 (0.1)	2 (0.2)	3 (0.2)	1.35	0.284	0.790
Acute respiratory failure	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.156
Dyspnoea	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.156
Hypoglycaemic coma	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.287
Hypoglycaemic unconsciousness	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.287
Osteomyelitis	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.214
Radius fracture	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.287
Septic shock	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.156
Syncope	0 (0.0)	2 (0.2)	2 (0.1)	NC	NC	0.214
Acute myocardial infarction	3 (0.4)	1 (0.1)	4 (0.2)	0.30	0.401	0.251
Transient ischaemic attack	3 (0.4)	1 (0.1)	4 (0.2)	0.20	0.599	0.145
Angina unstable	1 (0.1)	1 (0.1)	2 (0.1)	0.72	0.220	0.843
Appendicitis	1 (0.1)	1 (0.1)	2 (0.1)	0.57	NC	0.684
Cataract	1 (0.1)	1 (0.1)	2 (0.1)	1.00	NC	0.998
Depression	1 (0.1)	1 (0.1)	2 (0.1)	0.57	NC	0.684
Fall	1 (0.1)	1 (0.1)	2 (0.1)	1.00	NC	0.998
Headache	1 (0.1)	1 (0.1)	2 (0.1)	0.57	NC	0.684
Hypertension	1 (0.1)	1 (0.1)	2 (0.1)	1.00	NC	0.998
Peritonsillar abscess	1 (0.1)	1 (0.1)	2 (0.1)	0.57	NC	0.684
Spinal compression fracture	1 (0.1)	1 (0.1)	2 (0.1)	0.78	0.103	0.843
Ankle fracture	2 (0.3)	0 (0.0)	2 (0.1)	0.00	NC	0.060
Aortic stenosis	2 (0.3)	0 (0.0)	2 (0.1)	0.00	NC	0.060
Coronary Artery stenosis	2 (0.3)	0 (0.0)	2 (0.1)	0.00	NC	0.158
Gastrointestinal haemorrhage	2 (0.3)	0 (0.0)	2 (0.1)	0.00	NC	0.158
Myocardial infarction	2 (0.3)	0 (0.0)	2 (0.1)	0.00	NC	0.158
Pulmonary embolism	2 (0.3)	0 (0.0)	2 (0.1)	0.00	NC	0.158
Pyelonephritis acute	2 (0.3)	0 (0.0)	2 (0.1)	0.00	NC	0.158

Source: Summary of Clinical Safety Table 2.7.4.14

Table 8: Adverse Events Reported as Reason for Discontinuation from IP in Week 52 Safety Populations from ITRM and ITRN

Preferred Term	Humalog (N=779) n	Humalog (N=779) (%)	All LY (N=1116) n	All LY (N=1116) (%)	Total (N=1895) n	Total (N=1895) (%)	OR*b	Heterogeneity P-value*c	P-value*d
Subjects with >=1 AE	8	(1.0)	19	(1.7)	27	(1.4)	1.65	0.724	0.230
Maternal exposure before pregnancy*a	2	(0.6)	5	(1.0)	7	(0.8)	1.34	NC	0.727
Acute myocardial infarction	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.317
Anaemia	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Back pain	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.317
Colon cancer	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Death	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Ecchymosis	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Hepatitis C	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.317
Hypoglycaemia	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Injection site oedema	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.317
Localised infection	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Multiple injuries	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Renal neoplasm	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.317
Septic shock	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.317
Sleep disorder	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Aortic stenosis	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.184
Confusional state	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.184
Gastrointestinal haemorrhage	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.318
Multiple fractures	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.318
Rash macular	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.184
Sudden death	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.318

Abbreviations: IP = Investigational Product; All LY = LY900014 administered 0-2 minutes prior to the start of the meal or administered 20 minutes after the start of a meal; N = number of subjects in analysis population; n = number of subjects with events meeting specified criteria; NC = Not Calculable.
*a - Denominator adjusted because gender-specific event for females: N=348(Humalog), N=500(All LY)
*b – Mantel-Haenszel Odds Ratio stratified by study. All LY is numerator
*c – Heterogeneity of odds ratios across studies was assessed using the Breslow Day test
*d – p-values are from Cochran-Mantel-Haenszel (CMH) test of general association stratified by study. MedDRA Version 21.1
Source: ISS Table ISS.4.12

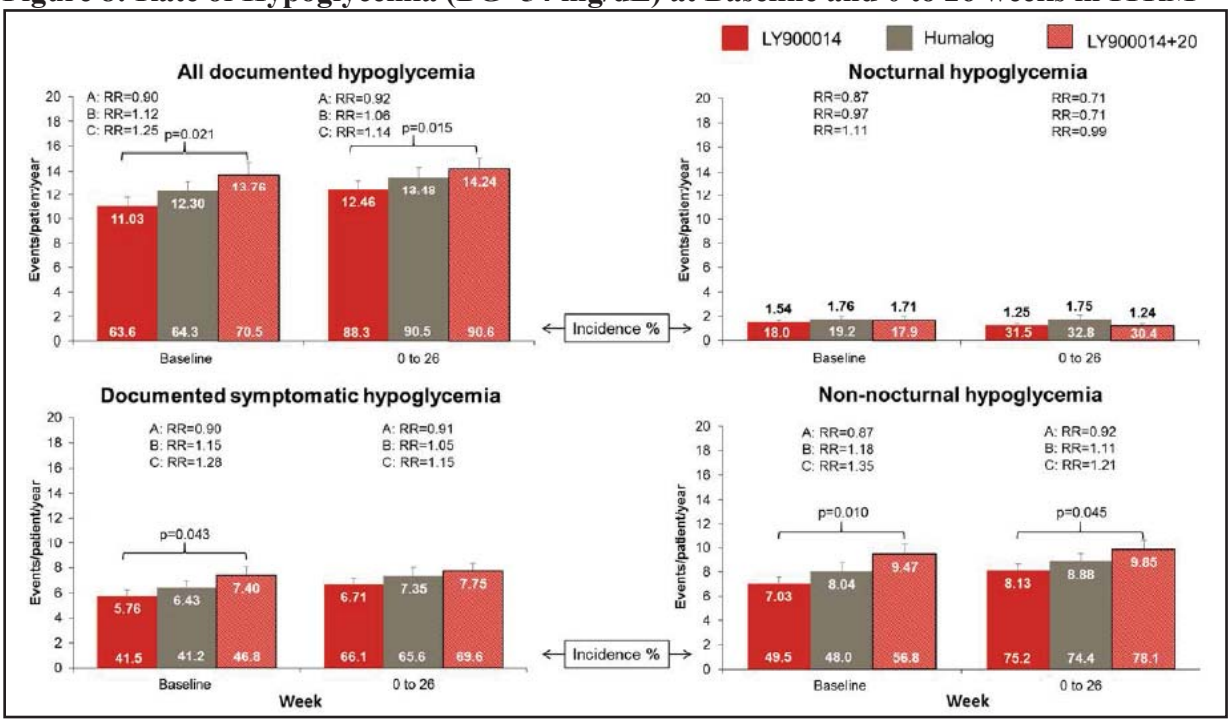
Dr. Misra evaluated hypoglycemia separately in the two pivotal MDI studies, due to differences in the study populations (i.e., T1D vs T2D) and differences in the dosing regimens (i.e., the inclusion of a postmeal treatment arm in ITRM). Dr. Misra focused her review on the incidence and rates of severe hypoglycemia and documented clinically significant hypoglycemia with blood glucose <54 mg/dl (with and without symptoms). See Table 9, Table 10, Figure 8, Figure 9, and Figure 10.

Table 9: Summary of Severe Hypoglycemia Rate and Incidence from Randomization to Week 26 - Study ITRM Safety Population

Treatment	Rate				Incidence			
	Mean (SD)	Aggregate Rate/100 Years	p-value[a] vs Humalog	p-value[a] vs LY900014	(%)	Episodes	p-value[b] vs Humalog	p-value[b] vs LY900014
Humalog (N=442)	18.48 (103.90)	18.34	-	-	25 (5.66)	40	-	-
LY900014 (N=451)	17.04 (84.34)	16.50	0.764	-	25 (5.54)	37	0.941	-
LY900014+20 (N=329)	21.15 (168.38)	13.70	0.454	0.610	15 (4.56)	22	0.517	0.559

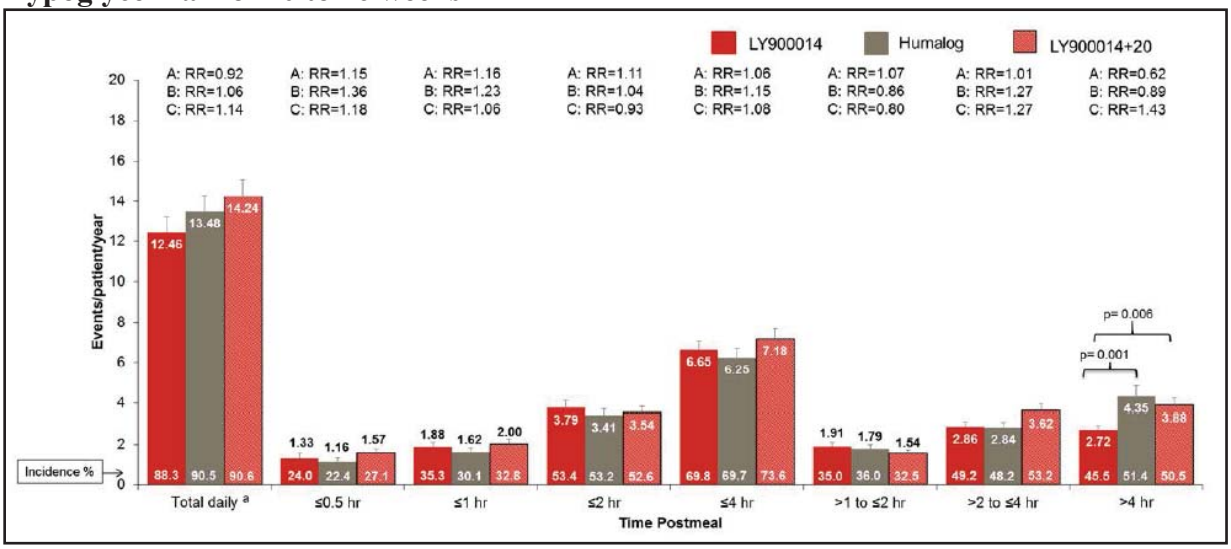
Abbreviations: N = number of patients in the population with baseline and post-baseline value at the specified time point: n = number of patients with hypoglycemia; SD = standard deviation. a p-value is from empirical variance estimation for the event rate, and is for comparison of aggregate rates, b p-value is from logistic regression model with term for treatment. Note: The aggregate rate was calculated using the total number of severe hypoglycemia episodes divided by the cumulative days on treatment from all patients within a treatment group, times 36525 (for rate per 100 years).
Source: Summary of Clinical Safety Table 2.7.4.17

Figure 8: Rate of Hypoglycemia (BG<54 mg/dL) at Baseline and 0 to 26 weeks in ITRM



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. Event rate data are LSM (SE). **Source: Summary of Clinical Safety Figure 2.7.4.1**

Figure 9: Rate and Incidence of Documented Symptomatic and Asymptomatic Postmeal Hypoglycemia from 0 to 26 weeks in ITRM



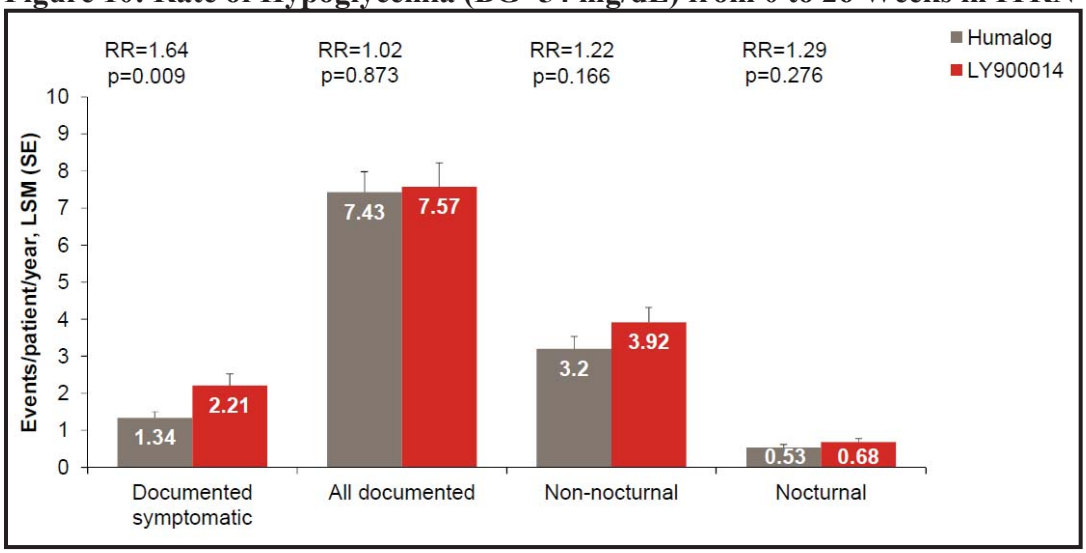
Abbreviations: A = LY900014/Humalog; B = LY900014+20/Humalog; BG = blood glucose; C = LY900014+20/LY900014; LSM = least squares mean; RR = relative rate; SE=standard error. Data are LSM (SE)
a Rate of daily all documented hypoglycemia. **Source: CSR ITRM Figure ITRM.12.6**

Table 10: Summary of Severe Hypoglycemia Rate and Incidence from Randomization to Week 26 in ITRN Safety Population

		Rate			Incidence		
		Aggregate					
Treatment	N	Mean (SD)	Rate 100 Years	p-value[a]	n (%)	Episodes	p-value[b]
Humalog	337	4.15 (32.49)	4.19	0.467	6(1.78)	7	0.350
LY900014	336	2.37 (26.53)	2.44		3 (0.89)	4	

Abbreviations: N = number of patients in the population with baseline and post-baseline value at the specified time point: n = number of patients with hypoglycemia; SD = standard deviation. a P-value is from empirical variance estimation for the event rate, and is for comparison of aggregate rates, b Logistic regression model for postbaseline comparisons between treatment and control groups: Incidence = Treatment. Note: The aggregate rate is calculated using the total number of severe hypoglycemia episodes divided by the cumulative days on treatment from all patients within a treatment group, times 36525 (for rate per 100 years). **Source: Summary of Clinical Safety Table 2.7.4.23**

Figure 10: Rate of Hypoglycemia (BG<54 mg/dL) from 0 to 26 Weeks in ITRN



Abbreviations: BG = blood glucose; LSM = least squares mean; RR = relative rate; SE = standard error.
Source: Summary of Clinical Safety Figure 2.7.4.5

Overall, Dr. Misra concluded that the hypoglycemia data from ITRM and ITRN show that LY900014 has a comparable safety profile to Humalog with response to postprandial hypoglycemia. She also concluded that, while ITRN did not investigate postmeal dosing of LY900014 in patients with T2D, that the reassuring hypoglycemia profile associated with postmeal dosing of LY900014 in ITRM supports a favorable benefit-risk assessment for postmeal dosing of LY900014 in the T2D population. She based this conclusion on her clinical opinion that adverse hypoglycemia findings associated with postmeal dosing would be more likely to have been observed in the T1D patient population. I concur with her assessment.

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

9. Pediatrics

BLA 761109 triggers PREA. The Applicant reached agreement with FDA on December 4, 2017 on the initial Pediatric Study Plan (iPSP) for LY900014 under IND 127210. Partial waivers were granted for pediatric patients with T1D less than one year of age because studies are impossible or highly impracticable and for pediatric patients less than 10 years of age because the product fails to represent a meaningful therapeutic benefit over existing therapies and because it is unlikely to be used in a substantial number of all pediatric age groups. A pediatric deferral was requested for its clinical study (ITSB) in children with T1D older than one year of age; ITSB was initiated on April 7, 2019. As described below, PMR 3874-1 will be issued with the approval of BLA 761109 to ensure the completion of Study ITSB.

No clinical studies are planned in children with T2D. (b) (4)

10. Other Relevant Regulatory Issues

OSI Site Inspections: Cynthia Kleppinger from OSI conducted the review of the inspections for the clinical sites for BLA 761109. The inspections included two domestic and three foreign clinical sites. The inspection of one clinical investigator revealed regulatory deficiencies, which are unlikely to have a significant impact on overall safety and efficacy results. The inspection of the remaining investigators and of the Applicant reveal no regulatory violations. Dr. Kleppinger concluded, and I concur, that the inspectional findings support the validity of the data reported by the Applicant under BLA 761109.

Proprietary Name: Ariane Conrad from DMEPA reviewed the proposed proprietary names Lyumjev, Lyumjev KwikPen, Lyumjev Junior KwikPen, and Lyumjev Tempo Pen for review on December 13, 2019. After review, Dr. Conrad determined (and I concur) that the proposed proprietary names are acceptable.

Non-proprietary Name: Carlos Mena-Grillasca from DMEPA reviewed the proposed four-letter suffixes for inclusion in the non-proprietary name. DMEPA concluded, and I concur, that the suffix -aabc is acceptable and that the non-proprietary name will be insulin lispro-aabc.

11. Labeling

Human Factors: Janice Purcell evaluated the human factors (HF) differentiation study results. The HF differentiation study sought to demonstrate that LY900014 pre-filled pens can be differentiated from other products that users may take concurrently. The review of the study revealed six instances where patients selected the wrong pen injector. However, it does not appear that any of the selection errors were due to the user interface; it was therefore determined that no changes to the user interface were warranted. The evaluation did identify areas of vulnerability that may lead to medication errors. Recommendations were provided to

the Applicant to implement, as it was determined that the changes can be implemented without additional validation testing.

DMEPA: Ariane Conrad reviewed revised container labels and carton labeling received on May 27, 2020 and June 4, 2020 to determine if they are acceptable from a medication error perspective. The revisions were made in response to recommendations previously provided. The review determined that the Applicant implemented all of the recommendations.

OPDP and Patient Labeling: Ankur Kalola from the Office of Prescription Drug Programs (OPDP) and Nyedra Booker from the Division of Medical Policy Program (DMPP) – in conjunction with reviewers from DDLO – provided recommendations to the Applicant for the proposed prescribing information (PI), patient package inserts (PPI), and Instructions for Use (IFUs). The Applicant implemented acceptable revisions to the PI, PPI, and IFUs to address the recommendations.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend **Approval**

- Post-marketing requirements:

I recommend issuing a post-marketing requirement to ensure completion of the clinical study (ITSB) in children with T1D older than one year of age for which the Applicant requested a pediatric deferral.

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).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
06/15/2020 02:25:37 PM