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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Dolly Misra, MD
BLA 761109
Lyumjev, insulin lispro

CLINICAL REVIEW

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(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
Applicant Proposed Indication(s)/Population(s)	To improve glycemic control in adults with diabetes mellitus
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults with diabetes mellitus

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Glossary

AC	advisory committee
ADA	anti-drug antibody
AE	adverse event
AIA	anti-insulin antibody
AR	adverse reaction
β -cell	beta cell
BE	bioequivalence
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSII	continuous subcutaneous insulin infusion
CSR	clinical study report
CSS	Controlled Substance Staff
DDI	drug-drug interaction
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FCDP	fixed combination dose product
FDA	Food and Drug Administration
GCP	good clinical practice
GD	glucodynamic
G_{tot}	total glucose infused
GIR	glucose infusion rate
GRMP	good review management practice
HbA1c	hemoglobin A1c
ICH	International Council for Harmonization

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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	intent to treat
IV	intravenous
IWRS	interactive web-response system
MDI	multiple daily injection
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	mixed-effect repeated measure model
MMTT	mixed-meal tolerance test
Nab	neutralizing antibody
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
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
PT	preferred term
R _{max}	maximum glucose infusion rate
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous

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SMBG	self-monitored blood glucose
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
tR _{max}	time to maximum glucose infusion rate

1. Executive Summary

1.1. Product Introduction

Lyumjev (insulin lispro-aabc), hereafter referred to as LY900014, is a new formulation of insulin lispro, developed by Eli Lilly and Company (Applicant), with the proposed indication to improve glycemic control in adults with diabetes mellitus. LY900014 is formulated with insulin lispro, which is also found in Humalog® (BLA 020563). Additionally, LY900014 incorporates (b) (4)

[REDACTED] treprostnil, (b) (4)
[REDACTED] and citrate (b) (4)

LY900014 will be made available in 2 dosage strengths, 100 units/mL (U-100) and 200 units/mL (U-200) as a solution for subcutaneous (SC) injection or for intravenous (IV) use under medical supervision. The U-100 preparation will be made available as a 10-mL vial, 3 mL-cartridge, and 3 prefilled pen options. The U-200 preparation will be available as a prefilled pen option. The Applicant proposes that dosing of LY900014 may occur by SC injection (b) (4) [REDACTED] within 20 minutes after starting a meal.

The Applicant submitted the proposed name Lyumjev for LY900014, and the Division of Medication Error Prevention and Analysis (DMEPA) reviewed and concluded that the name Lyumjev was conditionally acceptable on 2/13/2020. The Applicant submitted the proposed suffix aabc for the nonproprietary name, insulin lispro-aabc, and DMEPA deemed insulin lispro-aabc conditionally acceptable on 2/21/2020.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has submitted a 351(a) biologics license application (BLA) for LY900014. The submission includes the efficacy results and safety data from two Phase 3, prospective, multinational, randomized, double-blind, active-controlled trials: one conducted in patients with type 1 diabetes (T1D) and another conducted in patients with type 2 diabetes (T2D). The primary objective of the studies was to demonstrate that treatment with mealtime LY900014 is noninferior to Humalog on glycemic control in patients receiving basal insulin, as measured by change in HbA1c from baseline to Week 26. The secondary objectives were to demonstrate superiority of mealtime LY900014 to Humalog in controlling 1-hour and 2-hour post-prandial glucose (PPG) excursions following mixed meal tolerance test (MMTT) at Week 26, and superiority of mealtime LY900014 to Humalog on glycemic control. The demonstration of noninferiority of dosing with LY900014 20 minutes after meals to mealtime Humalog on glycemic control in T1D patients was also a secondary objective. For purposes of drug approval

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and labeling, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) relies on demonstration of efficacy based upon reduction in HbA1c, a well-validated surrogate for efficacy, to support an indication of glycemic control. Since the clinical significance of reduction in postprandial glucose excursions is yet not established, DDLO considers change in this parameter as an exploratory endpoint.

Both studies compared the efficacy of treatment with mealtime LY900014 to Humalog in a double-blind fashion. In the T1D population, the efficacy of treatment with LY900014 administered 20 minutes after meals was investigated in an open-label arm. The results of these pivotal studies were successfully able to demonstrate noninferiority of mealtime LY900014 to Humalog in change in HbA1c from baseline to Week 26 in both the T1D and T2D populations. In the T1D population, noninferiority on glycemic control was also demonstrated with treatment with LY900014 administered 20 minutes after meals. Both studies also demonstrated the superiority of LY900014 to Humalog in controlling 1-hour and 2-hour PPG excursions, although the clinical relevance of this finding is of unknown significance. While treatment with mealtime LY900014 was found to be statistically superior to Humalog on glycemic control in the T1D study population, the treatment difference (point estimate of 0.08 with the upper bound of the confidence interval at 0) was not considered to be clinically significant. In addition, while similar, the basal insulin doses were not identical across study treatment arms – numerically, patients randomized to LY900014 received slightly higher doses than patients randomized to Humalog. Moreover, the superiority finding for the primary endpoint was not replicated in the T2D study population. For these reasons, DDLO determined that the superiority of LY900014 to Humalog was not established.

In summary, the results of these two adequate and well-controlled trials provide independent substantiation of efficacy in terms of change in HbA1c, which has been accepted by FDA as an established surrogate outcome measure of efficacy of anti-hyperglycemic agents.

1.3. **Benefit-Risk Assessment**

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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. There are two types of diabetes: 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 after multiple non-insulin antihyperglycemic medications 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. To fulfill this unmet need, a goal of drug development programs has been to formulate rapid acting insulin analogs which more closely mimic physiologic postmeal insulin secretion patterns of healthy subjects.

The Applicant has submitted a new biologics license application (BLA) for Lyumjev (LY900014). LY900014 is a new insulin lispro product that has been formulated (b) (4)

In support of this application, the Applicant has submitted the data from two pivotal trials, Study ITRM and Study ITRN, similar in design, investigating the efficacy and safety of treatment with mealtime LY900014 in comparison to Humalog (insulin lispro) for glycemic control in patients with T1D and T2D, respectively.

Study ITRM and Study ITRN were Phase 3, multinational, prospective, randomized, double-blind trials with the primary objective of demonstrating that treatment with mealtime LY900014 is noninferior to Humalog on glycemic control in patients receiving basal insulin, as measured by change in HbA1c from baseline to Week 26. The secondary objectives were to demonstrate superiority of mealtime LY900014 to Humalog in controlling 1-hour and 2-hour post-prandial glucose (PPG) excursions following mixed meal tolerance test (MMTT) at Week 26, and superiority of mealtime LY900014 to Humalog on glycemic control. Demonstrating noninferiority of postmeal dosing of LY900014 20 minutes after meals to premeal Humalog on glycemic control was also a secondary objective in the T1D study.

The analyses used to formulate my conclusions of efficacy and determine the data to be included in labeling are analyses which were conducted and/or corroborated by the FDA statistical reviewer. In these analyses, Intent to Treat (ITT) population included all randomized subjects who had at least one baseline assessment. A return to baseline multiple imputation approach was used to impute missing data.

Study ITRM and Study ITRN were both able to achieve their primary objectives by establishing noninferiority of treatment with mealtime LY900014 to Humalog on glycemic control, as measured by change in HbA1c from baseline to Week 26, in patients with T1D and T2D. The analyses showed that the upper bound of the two-sided 95% confidence interval (CI) for treatment difference (LY900014-Humalog) was less

than the pre-specified non-inferiority margin of 0.4%, as well as the more stringent noninferiority margin of 0.3%, in both trials. Although Study ITRM found the estimated treatment difference of mealtime LY900014 versus Humalog (95% CI) to be -0.08 [-0.16, 0.00], demonstrating statistical superiority, the estimated treatment difference was considered too small to constitute a clinically significant difference (especially in the context of basal insulin doses that were not identical across study treatment arms). Additionally, superiority was not replicated in Study ITRN (b) (4)

Postmeal dosing with LY900014, studied in the T1D population, also demonstrated efficacy. The estimated treatment difference of postmeal LY900014 versus Humalog (95% CI) was 0.14 [0.05, 0.22]. The result for postmeal LY900014 treatment was statistically inferior to mealtime Humalog, as the treatment difference and the upper and lower bounds of the 95% CI were above zero; however, this dosing regimen demonstrated noninferiority, with the upper bound of the two-sided 95% CI for treatment difference less than 0.4% and also less than 0.3%. The finding that postmeal LY00014 treatment is noninferior (i.e., clinically not unacceptably worse) to Humalog is sufficient to demonstrate efficacy. Postmeal dosing of LY900014 was not investigated in patients with T2D. Instead, the Applicant relied on the totality of the data from the Phase 3 studies, clinical pharmacology mealtime studies, and model-based simulations to support an extrapolation of efficacy of postmeal dosing in the T2D population. After review, the data from the Phase 3 studies, two clinical pharmacology mealtime studies (ITRV and ITRW), and the pharmacometric modeling were determined to be sufficient to support postmeal dosing of LY900014 in patients with T2D as well as patients with T1D.

Both Study ITRM and Study ITRN were also able to successfully achieve their secondary objectives, demonstrating statistical superiority of treatment with mealtime LY900014 to Humalog in 1-hour and 2-hour PPG excursion following MMTT after 26 weeks of treatment. While the treatment effect of LY900014 on PPG excursion compared to Humalog appears to be consistent, the interpretability of this finding in terms of clinical benefit is unclear. The link between a modifying effect on PPG excursions on clinical outcomes is not sufficiently strong to consider the use of this PD endpoint as a surrogate for efficacy. Additionally, the relative degree of PPG lowering that is clinically relevant has not been established. (b) (4) Nevertheless, the robustness and consistency of these exploratory findings from the data in both the T1D and T2D patients provide supportive evidence of the treatment effect of LY900014.

The results of Study ITRM and Study ITRN provide independent substantiation of efficacy in terms of change in HbA1c, which is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and 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.

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Similarly, the results of the Kumamoto Study¹⁴ showed that intensive insulin therapy resulting in better glycemic control (HbA1c < 7.1%) prevents the progression of microvascular complications in patients with T2D.

The safety findings for LY900014 during the clinical trials did not reveal any new safety signals or concerns than other insulin products. The known risks commonly associated with use of insulin include hypoglycemia, hypersensitivity, and injection site reactions. No difference in the incidence of potential hypersensitivity adverse events (AEs) was noted in the safety population. With the faster-time action profile and novel excipients in LY900014, the AEs of hypoglycemia and injection site reactions were examined more carefully. While the timing of postprandial hypoglycemia events with LY900014 was consistent with its faster PD profile, overall the number of hypoglycemic events observed with LY900014 was similar to Humalog. No significant differences were noted in the incidence of severe or clinically significant hypoglycemia for LY900014, whether dosed at mealtime or 20 minutes postmeal, in comparison to Humalog. The incidence of reported injection site reaction-related AEs was higher with LY900014 compared to Humalog. However, the majority of these AEs were transient, mild to moderate in severity, and did not interrupt or modify dosing during treatment and, therefore, do not pose a significant clinical concern. In comparison to another marketed faster-acting rapid insulin product formulated with other absorption enabling excipients, the AE profile is similar for LY900014.

The conclusions from other FDA disciplines reviewing the BLA for LY900014 are also supportive of the efficacy and safety of LY900014. It was noted, however, in the Product Quality review, that compatibility testing for the intravenous (IV) administration of LY900014 was not sufficient to exclude the possibility of variable insulin delivery at concentrations below 1 U/ml. To mitigate the risk of variable insulin delivery with IV administration at lower dilutions, the instructions for IV use in the label should be modified to state that dilutions below 1 U/mL are not recommended.

In summary, the benefit of LY900014 is supported by the results of two adequate and well-controlled trials that demonstrated efficacy in terms of change in HbA1c, which has been associated with improved clinical outcomes in patients with diabetes. The safety analyses of the data from these studies show that LY900014 has a safety profile similar to other rapid acting marketed insulin products, suggesting that LY900014 is safe, and poses no new or significantly increased risks to patients requiring insulin therapy. Based on the totality of evidence, I believe that benefit-risk assessment for LY900014 is favorable, and I recommend approval of LY900014 for the indication to improve glycemic control in adults with diabetes mellitus. I also support the flexibility of dosing proposed in the label for LY900014 subcutaneous injection at the start of a meal or within 20 minutes after starting a meal.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	• 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.	Both T1D and T2D are serious, life-threatening conditions that can lead to serious morbidity and mortality if left untreated.
<u>Current Treatment Options</u>	• The results of the Diabetes Control and Complications Trial (DCCT)^{4,5,6} 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 pancreatic beta cells which produce insulin, patients with T1D require exogenous insulin for survival. Pramlintide, an amylin-mimetic, is also approved as adjunctive therapy to insulin. • Treatment options for T2D include lifestyle modifications, usually	Intensive insulin therapy is the standard of care for patients with T1D. Patients with T2D often require multiple agents for glycemic control, and due to the progressive nature of the disease, may also require insulin to achieve glycemic targets.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	followed by the addition of one or multiple different medications⁷. There are currently multiple classes of pharmacologic treatments for T2D, 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, and sodium-glucose linked transporter (SGLT)-2 inhibitors.	
<u>Benefit</u>	• Study ITRM demonstrated that administration of LY900014 at mealtime is noninferior to Humalog in change in HbA1c from baseline to Week 26 in patients with T1D. Although found to be statistically superior, the treatment difference (point estimate of 0.08 with the upper bound of the confidence interval at 0) was not considered to be clinically significant. • Although statistically significantly inferior, LY900014 dosed 20 minutes postmeal was also shown to be noninferior (clinically not unacceptably worse) to Humalog in change in HbA1c from baseline to Week 26 in Study ITRM. • Study ITRN demonstrated that mealtime LY900014 is noninferior to Humalog in change in HbA1c from baseline to Week 26 in patients with T2D. • Both ITRM and ITRN showed that mealtime LY900014 is superior to Humalog in 1-hour and 2-hour PPG excursion following MMTT; however, the statistically significant improvement in PPG was not accompanied by a clinically significant difference in treatment effect on HbA1c. The clinical significance of PPG reduction, independent of HbA1c reduction, has not been established and therefore, these data are considered exploratory and only supportive of efficacy.	The demonstration of noninferiority of treatment with LY900014 to Humalog in change in HbA1c in these two Phase 3 clinical trials support the efficacy of LY900014 when dosed at mealtime in T1D and T2D, and when administered postmeal in T1D Study ITRN did not investigate postmeal dosing of LY900014 in patients with T2D. However, a data package comprising the Phase 3 studies, two clinical pharmacology mealtime studies, and model-based simulations were deemed sufficient to support an extrapolation of the efficacy of postmeal dosing demonstrated in the T1D population to the T2D population. While mealtime LY900014 administration demonstrates superiority to Humalog in PPG excursion following MMTT in both T1D and T2D patients, the interpretability of this finding

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Clinical pharmacology Study ITRW showed that PPG excursion over 5 hours following MMTT does not differ between LY900014 dosed 20 minutes postmeal and mealtime Humalog in patients with T2D. • Although only Trial ITRM in patients with T1D investigated postmeal dosing with LY900014, it is acceptable to extrapolate data from T1D study to the T2D population as the T2D population is less insulin sensitive and any adverse findings would be more apparent in the T1D population. • The totality of the data support the approval of LY900014 for the indication to improve glycemic control with adults with diabetes mellitus and, also support the administration of LY900014 at the start of a meal or within 20 minutes after starting a meal.	in terms of clinical benefit is unclear. The link between a modifying effect on PPG excursions on clinical outcomes is not sufficiently strong to consider the use of this PD endpoint as a surrogate for efficacy. While, the consistency of these findings is supportive evidence of the treatment effect of LY900014 in both the T1D and T2D populations, (b) (4) HbA1c is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus. Thus, the demonstration of noninferiority of treatment with LY900014 to Humalog on change in HbA1c from these two adequate and well-controlled trials provides substantial evidence of efficacy and is the basis of approval and labeling of LY900014.
<u>Risk and Risk Management</u>	• The safety profile of LY900014 was found to be similar to Humalog and other insulin products. • The safety data did not suggest a different risk of hypoglycemia than Humalog in either the T1D or T2D populations. • LY900014 was associated with a higher risk of AEs related to injection	The proposed label adequately relays the safety risks associated with LY900014 and insulin therapy. The labeling for instructions of IV

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	site reactions; however, the severity of reactions was mild to moderate and transient in nature and did not require dosage adjustment or discontinuation of product in the majority of patients. • Compatibility testing for the IV administration of LY900014 was not sufficient to exclude the possibility of variable insulin delivery at concentrations below 1 U/ml.	administration of LY900014 will be modified to state that dilutions below 1 U/mL are not recommended.

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1.4. Patient Experience Data

The patient experience data submitted as part of this application included a patient perspective study titled, Perspectives of People with Diabetes: Mealtime Insulin Experience. This cross-sectional, non-interventional, qualitative study involved 30 adult participants with T1D or T2D on mealtime insulin (MTI) from the United States and United Kingdom. Participants completed a 90-minute, semi-structured web conferencing interview with questions designed to elicit participant's experiences around MTI and associated blood glucose control.

The objectives of the study were to understand patients' unmet needs related MTI therapy including: barriers and advantages; symptoms and impacts; and relevant treatment outcomes. Patients most commonly identified ease of use, flexibility, and convenience as being advantages of prandial insulins. Frequency of dosing, psychosocial factors related to dosing in public, and discomfort from injecting were reported most often as the disadvantages of MTI therapy. The negative effects associated glycemic fluctuations reported by patients included psychological/mood (72%), social (63%), work/school (54%), and sleep (52%) perturbations. While a patient's HbA1c level is the clinical measure used to assess the adequacy of glycemic control, only 10% of the study participants reported having an HbA1c below 7%, and over 16% did not know their HbA1c levels. Participants defined treatment success with prandial therapy as having glucose levels stay in range by taking the appropriate amount of insulin and not experiencing hyperglycemia and hypoglycemia.

The authors conclude that traditional assessments used for defining successful diabetes management may not encompass important issues from the patient's perspective. The findings of this study demonstrate that diabetic patients experience an extensive range of symptoms and impacts on their daily living while receiving their current treatment regimens. While HbA1c is the standard endpoint for clinical trials in diabetes, many patients are unaware of their HbA1c levels and do not perceive changes in these levels. Instead, blood glucose fluctuations which result in psychological, mood, and physical symptoms are reported to be of greater concern to patients. Successful therapy, from a patient's perspective, is focused more on consistent glycemia with fewer episodes of hypoglycemia and hyperglycemia. Therefore, the authors assert that salient measures beyond HbA1c assessment should be considered when evaluating treatment satisfaction and outcomes among patients with diabetes.

Reviewer Comment: *This 30-patient study assessing the perspectives of diabetic patients receiving MTI revealed, not surprisingly, that the daily goals of diabetes management include stabilization of glycemic variability to minimize the impact of glucose fluctuations on physical, emotional, and psychological well-being. The participants of this small study were not involved with LY900014 clinical trials; therefore, these study findings were not used to support conclusions of effectiveness.*

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

X	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	
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
X	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	
	☐ 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	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
	☐ 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 2017 National Diabetes Statistics Report from the Centers for Disease Control (CDC) estimates that 30.3 million Americans (9.4 % of the US population) are currently living with diabetes¹. Both T1D and T2D are serious chronic disorders characterized by hyperglycemia.

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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.

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) complications². Results from the Diabetes Control and Complication Trial (DCCT)³⁻⁹, United Kingdom Prospective Diabetes Study (UKPDS)^{2, 10-13} and the Kumamoto Study¹⁴ suggest that improved glycemic control (as measured by HbA1c) result in improved outcomes.

2.2. Analysis of Current Treatment Options

Patients with T1D have minimal or no residual pancreatic islet beta cell function and are therefore dependent on exogenously administered insulin for survival. Insulin is available in a variety of formulations and analogs, with a spectrum of time-action profiles. Long acting, or basal insulin, is generally administered as one or two injections daily. Short-acting, or prandial insulin, is typically administered before each meal. An insulin pump device is an alternate insulin delivery option offering continuous subcutaneous basal insulin infusion with mealtime boluses. Pramlintide, an amylin analog, may also be added to insulin regimens in patients with T1D.

Patients with T2D may be managed with a combination of proper diet, exercise, and one or more drug products. There are currently 12 pharmacological classes of medications approved in the US to treat diabetes. Many of these antihyperglycemic agents (AHA) are also approved as fixed combination dose products (FCDPs). A listing of therapeutic options for the management of diabetes is presented in **Table 1**. FCDPs and injectable insulin plus non-insulin FCDPs are not listed.

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Table 1: Approved Therapeutic Options for the Management of Diabetes Mellitus*

Pharmacologic Class	Antihyperglycemic Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Miglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-4 INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide; Lixisenatide, Semaglutide
INSULINS AND INSULIN ANALOGUES	Inhaled insulin human; Insulin aspart; Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin lispro; Insulin regular (human); Pre-mixed insulins (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT2 INHIBITORS	Canagliflozin; Dapagliflozin; Empagliflozin, Ertugliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glipizide extended-release; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

***Note:** Only insulins, insulin analogues, and amylin mimetics are approved for T1D.

Source: Drugs@FDA: FDA Approved Drug Products, available at: <http://www.accessdata.fda.gov/scripts/cder/daf/>.

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Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter 2.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

LY900014 and Humalog are both formulated with insulin lispro. Humalog (BLA 020563) was approved on June 14, 1996 and is indicated to improve glycemic control in adults and children with diabetes mellitus. The U-200 concentration of Humalog was approved for use on May 26, 2015.

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 key regulatory interactions between the Applicant and the Agency is provided below.

December 1, 2015: Type B Meeting Written Responses were issued. Pre-Investigational New Drug Application (PIND) was filed for LY900014. Lilly was advised that a separate assessment justifying a waiver of carcinogenicity studies for treprostinil should be provided. Additionally, Lilly was advised to characterize the systemic exposure of treprostinil in the planned key Phase 1 pharmacokinetic (PK) and pharmacodynamic (PD) studies, at the relevant clinical dose range, to determine the need to investigate the effect of hepatic impairment and drug-drug interactions (DDI).

April 29, 2016: Type C Meeting Written Responses were issued. FDA agreed to waive the requirement for rodent carcinogenicity studies for treprostinil to support approval of LY900014 based on review of findings that minimal systemic treprostinil exposure is expected with therapeutic use of LY900014.

January 25, 2017: Type C Meeting Written Responses were issued. FDA agreed that the nonclinical safety assessment of local tolerance with the commercial formulation of LY900014 would not be necessary based on review of safety findings of the Phase 1 Study 8330894, given the similarity of the composition of the LY900014 commercial formulation with the formulation evaluated in Study 8330984.

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March 21, 2017: Type C Meeting Written Responses were issued. FDA agreed that Lilly's anti-insulin lispro assay for use in for immunogenicity sampling in the pivotal clinical studies of LY900014 appear to be validated and acceptable.

April 19, 2017: Type B Meeting End of Phase 2 Meeting occurred. Discussions included the following:

- Non-clinical data appeared to be adequate to support submission of marketing application and juvenile animal toxicity study would not be necessary to support investigations in the pediatric population.
- Clinical pharmacology development plan appeared adequate and should also include a dose-response PK/PD study with minimum of 3 dose levels comparing to-be-marketed LY900014 to Humalog to support that PK/PD differences are preserved over clinically relevant dose ranges for dosing in Phase 3 trials.
- FDA agreed that hepatic impairment, renal impairment, and DDI studies were not required for LY900014 as data from Humalog was adequate.
- FDA agreed that bioequivalence (BE) study could support registration of the 200 units/mL concentration of LY900014. FDA requested analysis of additional PK and PD parameters (t_{max} , early 50% t_{max} , tR_{max} and early 50% tR_{max}).
- FDA agreed to the design of the Phase 3 multiple daily injection (MDI) studies (ITRM and ITRN) and with the 26-week primary endpoint.
- FDA agreed to the non-inferiority margin (NIM) of 0.4% for comparison of LY900014 to Humalog in both Studies ITRM and ITRN.
- FDA required that Study ITRM be completed to 12 months and that the immunogenicity follow-up data be provided in the initial BLA and 120-day safety update.
- FDA reviewed plans for treatment-emergent anti-drug antibody responses, cut-points for the assay (based on a 1% false positive rate), and use of MSR to define "treatment-boosted" population and "return to baseline." After discussion, the FDA proposed that Phase 1 studies could be utilized to assess differences in PK in patients who had anti-drug antibodies present at baseline.
- FDA agreed that post-meal dosing, at 20 minutes after the start of the meal, could be evaluated in Study ITRM and specified that the timing of the post-meal dosing be consistently administered at 20 minutes after the start the meal (rather than up to 20 minutes after the start of the meal) in order to clearly differentiate the timing of administration.
- FDA advised Lilly that if they intended not to study postmeal administration of LY900014 in the T2D population, they must provide justification why the timing of administration can be extrapolated to the T2D population, provided that postmeal administration is sufficiently supported in the T1D study.
-  (b) (4)

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(b) (4)

December 4, 2017: FDA agreed to the initial Pediatric Study Plan (iPSP), which includes a pediatric PK study (Study ITSA), followed by a safety and efficacy study (Study ITSB).

December 13, 2017: Type C Meeting regarding

(b) (4)

January 17, 2018: Type B meeting CMC preliminary comments for EOP2 issued. FDA agreed that treprostinil, as used in the final commercial formulation of LY900014, should be classified as an excipient. FDA agreed that the use of reversed phase high performance liquid chromatography (RP-HPLC) was acceptable to assess potency of LY900014 drug product.

April 23, 2018: Type C Meeting Written Responses were issued. Advice regarding pediatric Phase 3 Study ITSB and Statistical Analysis Plan was provided. Lilly was advised that use of flash glucose monitoring to collect glucose measurements for pediatric population should preferably be conducted with a device with approved indication for use in pediatric population; otherwise, the information from the device should not be used for clinical decision-making. Additionally, if the sponsor is seeking indication for post-meal dosing of LY900014 in pediatric patients, then Study ITSB should also include an arm assessing post-meal dosing. Lilly was also advised that if they plan to submit a Written Request to request exclusivity, then their planned Pediatric Study Request should include plan to assess safety and efficacy of LY900014 in insulin pump use in pediatric patients and in pediatric patients with type 2 diabetes.

August 27, 2018: Type C Meeting Written Responses were issued providing advice on the logistics of the BLA application.

May 22, 2019: Type B Meeting Pre-BLA meeting occurred. Discussions included the following:

- FDA agreed that the data package proposed by Lilly to support extrapolation of post-meal dosing to the T2D patient population [i.e., results of the Phase 3 Study ITRM in T1D, the clinical pharmacology studies (b) (4), ITRV, and ITRW), and model-based simulations] appeared adequate.

(b) (4)

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- FDA advised Lilly [REDACTED] (b) (4)

August 15, 2019: BLA 761109 for LY900014 U-100 and LY900014 U-200 was filed.

3.3. Foreign Regulatory Actions and Marketing History

LY900014 has not been approved for marketing in any country.

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 Cynthia Kleppinger, MD dated 4/7/2020. The audit involved clinical investigator site inspections for the sponsor as well as two domestic and three foreign clinical sites involved in the two phase 3 trials. The five sites selected had not previously been inspected and were flagged as having one or more of the following criteria: lower than average number of adverse events (AEs), higher than average rate of protocol violations, high number of serious adverse events (SAEs), and higher than average site-specific efficacy effect size. Results of the audit revealed that the sponsor and four of the sites overall demonstrated adequate adherence to the regulations and the investigational plan, resulting in no reports of notable objectionable conditions. For one investigator/clinical site (Wendell R. Miers, MD/ Kentucky Diabetes Endocrinology Center), a Form FDA-483, Inspectional Observations, was issued for failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, the ECG tracing for a study participant Subject [REDACTED] (b) (6) dated [REDACTED] (b) (6), was not consistent with the time planned for this screening activity and appeared to be the tracing of a subject involved in another study. Further investigation revealed the discrepancy to be the result of human error, and no fraud was suspected with this isolated occurrence. Based on cumulative information obtained from these five clinical site and sponsor inspections, Dr. Kleppinger's review concluded that the inspectional findings support validity of data as reported by the sponsor under this BLA.

4.2. Product Quality

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The drug substance, insulin lispro, used in the LY900014 formulation is manufactured in Indianapolis, IN, and the manufacturing process was previously approved under the application for Humalog. The commercial insulin lispro drug substance and LY900014 drug product manufacturing processes have been validated to consistently produce product that is pure, potent, and safe and is comparable to drug product used in clinical studies. The drug product used in the clinical drug development program for LY900014, including the Phase 3 studies and U-100 and U-200 bioequivalence study, is the same as the 'to be marketed' product.

The review of compatibility testing for the IV administration of LY900014 raised a clinical concern about the variability of insulin delivery when diluted to lower concentrations. In the studies performed to support that LY900014 is compatible with bags and tubing sets for IV administration, drug product was diluted according to the proposed labeling to 1 U/mL or 0.1 U/mL in either a 5% dextrose solution (D5W) or in normal saline (NS), and recoverable protein was assessed at various time-points up to 14 days after dilution. The data showed that protein recovery was 0-41% for the 0.1 U/mL samples, irrespective of solutions or bags used, indicating that patients may receive 0-41% of the intended dose. For the 1 U/mL samples, protein recovery was ~80%.

An information request (IR) was sent to the Applicant requesting data from other lispro products. The original compatibility studies for LY900014 at both concentrations were repeated, and revealed the following:

- LY900014 diluted to 1 U/mL showed 87-94% protein recovery in D5W and 87-96% in NS
- Humalog diluted to 1 U/mL in NS showed 88-94% protein recovery; D5W was not used
- LY900014 diluted to 0.1 U/mL was showed highly variable protein recovery ranging from 30-83% depending upon the time and IV bag used
- Humalog diluted to 0.1 U/mL in NS showed 80-92% protein recovery; D5W was not used

In summary, protein recovery was comparable between LY900014 and Humalog when diluted to 1 U/mL. When diluted to 0.1 U/mL, the recovery of LY900014 was lower than Humalog and variable.

The Office of Product Quality (OPQ) was scheduled to conduct an on-site inspection of Lilly del Caribe's Quality System on April 7-15, 2020; however, due to restrictions related to the coronavirus pandemic, OPQ has instead initiated a paper-based inspection (document review). The information from this evaluation is pending at the time of my review. The review detailing the findings of the Chemistry, Manufacturing and Controls (CMC) assessment for LY900014 from OPQ will be completed by Vicky Borders-Hemphill, PharmD.

Reviewer comment: *There is no advantage to using LY900014 intravenously, as the IV administration of LY900014 would be expected to have the same PK and glucodynamic response as IV Humalog; therefore, the likelihood of IV use of LY900014 in clinical practice low. However, as a consequence of clinical concerns related to the findings of variable insulin delivery at lower*

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dilutions, the instructions for IV use in the label should be modified to state that dilutions below 1 U/mL are not recommended. Due to the uncertainty of insulin delivery at lower dilutions, if the Applicant seeks to pursue broader labeling for IV administration analogous to other insulin products, submission of new supportive data would be required.

4.3. Clinical Microbiology

The clinical microbiology assessment was pending at the time of my review. The microbiology review for LY900014 will be completed by Dr. Candace Gomez-Broughton of the Division of Microbiology Assessment.

4.4. Nonclinical Pharmacology/Toxicology

The formulation for LY900014 differs from Humalog by the addition of three components: sodium citrate (b) (4), treprostinil (b) (4) and magnesium chloride (b) (4). The nonclinical support for this BLA primarily consisted of an assessment of treprostinil, as lispro, the active component of LY900014, was previously evaluated in support of Humalog. The other excipients did not require further testing as the levels of these excipients used in the LY900014 formulation are in the range of other marketed parenteral products administered chronically.

Treprostinil is a prostacyclin analog with vasodilatory activity and is the active ingredient of marketed products (Remodulin, Orenitram, and Tyvaso) approved for use in the treatment of pulmonary arterial hypertension to systemically lower blood pressure. The Applicant conducted a series of nonclinical studies with treprostinil to establish that clinically relevant doses of LY900014 administered subcutaneously contain microdoses of treprostinil that are not detectable in the systemic circulation or associated with any systemic effects. The Agency agreed with the Applicant's assessment that the quantities of treprostinil present in the final commercial LY900014 formulation meet the criteria for an excipient.

The summary of the nonclinical safety findings with treprostinil were supportive of its use as an excipient in the formulation of LY900014. Safety pharmacology studies with treprostinil revealed no effects on respiratory or central nervous system functioning. Cardiovascular safety pharmacology studies in dogs revealed prolonged QT/QTc times only at multiples greater than 50-fold the clinical exposure to treprostinil in LY900014. In repeat-dose toxicity studies with LY900014 administered in high doses in the rat and dog models, the clinical signs considered related to the pharmacologic action of the drug were limited to the transient appearance of red discoloration of the skin on the face, ears, and forelimbs of test species. No adverse effects were seen on other parameters during the in-life phase of the studies or in tissues evaluated at necropsy. Genotoxicity revealed no evidence of mutagenicity and reproductive toxicity studies did not reveal effects on fertility or pre-natal/post-natal development. Increased post-

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implantation loss was observed in the rabbit, but only at an exposure many thousand-fold above the potential clinical exposure.

For further details of the preclinical pharmacology/toxicology data, refer to Dr. Daniel Minck's review dated 5/5/2020. Dr. Minck recommends approval of this BLA. Based on his review, Dr. Mink found no adverse toxicity caused by treprostinil at high doses and high exposure multiples relative to the levels expected with clinical exposure with the LY900014 formulation; therefore, its inclusion as an excipient does not poses a risk from a toxicologic perspective.

4.5. Clinical Pharmacology

At the EOP2 meeting, the Division agreed that a bioequivalence (BE) study could support registration of the U-200 concentration of LY900014. Also, at the EOP2 meeting the Applicant was advised that if they intended not to study postmeal administration of LY900014 in the T2D population, they must provide justification why the timing of administration can be extrapolated to the T2D population, provided that postmeal administration is sufficiently supported in the T1D study. At the pre-BLA meeting, the Applicant proposed the rationale to support postmeal dosing in T2D patients based on the results of postmeal dosing from Study ITRM in T1D, the clinical pharmacology studies ITRV and ITRW, and model-based simulations.

The information presented in my review summarizes the conclusions of the Clinical Pharmacology review team for the following information:

- support of LY900014 U-200 formulation from bioequivalence Study ITSS
- support of postmeal dosing of LY900014 in T1D and T2D from Study ITRV and ITRW
- the Applicant's pharmacometrics assessment
- mechanism of action, PD, and PK of LY900014 in **Sections 4.5.1, 4.5.2, and 4.5.3**

Additional details of the clinical pharmacology investigations are available in the Clinical Pharmacology Review completed by the Office of Clinical Pharmacology (OCP) review team (Suryanarayana Sista, PhD; Liang Li, PhD; Justin Earp, PhD; Manoj Khurana, PhD). OCP recommends approval of this BLA. Refer to the OCP review dated 5/6/2020 for additional details of these studies and the clinical pharmacology development program.

Support for LY900014 U-200 Formulation

Study ITSS: Bioequivalence of U-200 and U-100 formulations

In support of the U-200 formulation of LY900014, Study ITSS, was conducted to establish bioequivalence (BE) of LY900014 U-100 and U-200 formulations. This study 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, which investigated the comparative PK and

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glucodynamics (GD) of the LY900014 U-100 and U-200 formulations following administration of a single 15 U SC dose.

A comparison of the primary PK parameters for U-200 and U-100 showed that the ratios of U-200/U-100 were 1.01 for the $AUC_{(0-10h)}$, $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$, and 0.97 for C_{max} . The 90% CIs for all the ratios were contained within the BE limits (0.80, 1.25), demonstrating BE of U-200 versus U-100 formulations of LY900014. Variability of $AUC_{(0-\infty)}$ and C_{max} were similar between U-200 and U-100 formulations.

Assessment of GD parameters revealed comparable glucose infusion rate (GIR) versus time profiles following administration of 15 U doses LY900014 U-100 and U-200 formulations. Primary PD parameters for the two formulations were similar, as demonstrated by the ratios (U200/U100) of geometric LS means of 1.05 for the total glucose infused (G_{tot}) and 1.03 for the maximum glucose infusion rate (R_{max}), and 90% CIs that were contained within the BE limits (0.80, 1.25) for both G_{tot} and R_{max} .

Reviewer comment: Study ITSS established BE of U-100 and U-200 formulations to support the approval of the U-200 formulation of LY900014 in this BLA.

Support for Postmeal Dosing of LY900014

Studies ITRV & ITRW: LY900014 vs Humalog immediately before and 20 minutes after MMTT

Study ITRV was a Phase 1, randomized, patient- and investigator-blind, 2-treatment, 4-period crossover study in patients with T1D to evaluate the PK of insulin lispro following a single SC injection of LY900014 and Humalog. The study also compared the effect of administering LY900014 or Humalog immediately before and 20 minutes after the start of the meal on the GD response. Study ITRW was an identical study in patients with T2D. The following summary is excerpted from the Clinical Pharmacology Review of the data from these studies:

Consistent with the observations from the Euglycemic Clamp PK/PD studies, LYUMJEV demonstrated accelerated insulin lispro absorption, reduced late insulin lispro exposure, and shorter exposure duration in T1D and T2D patients as compared to Humalog.

- **T1D Patients:** When LYUMJEV and Humalog were administered immediately before the start of the meal, LYUMJEV had a greater reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal compared to Humalog. The reduction in change from baseline postprandial glucose excursion up to 4 hours post-meal was not statistically significant when LYUMJEV and Humalog were administered 20 minutes after the start of the meal. Similarly, the postprandial glucose excursion over the 5-hour MMTT was similar between LYUMJEV and Humalog when LYUMJEV was dosed 20 minutes after the start of the meal and Humalog was dosed immediately before the start of the meal.
- **T2D Patients:** When LYUMJEV and Humalog were administered immediately before the start of the meal, LYUMJEV had a greater reduction in change from baseline postprandial

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

The clinical pharmacology reviewer concluded that with regard to the dosing regimen, “The proposed time of injection for LYUMJEV at start of the meal or within 20 minutes after starting a meal, in comparison to Humalog (injection within 15 minutes before a meal or immediately after a meal) is supported by data from PK/PD studies and the Clinical evaluation of this time of injection and doses, which demonstrate that LYUMJEV was noninferior to Humalog on glycemic control in patients with T1D and T2D, when administered as prandial insulin per the claimed time of injection, in combination with basal insulin glargine or insulin degludec for 26 weeks” (see Clinical and Statistical reviews for further details).

Pharmacometrics Assessment

The following information is summarized from the Clinical Pharmacology review of the Applicant’s pharmacometrics assessment.

The Applicant’s population PK analysis was conducted based on 18,957 evaluable insulin lispro concentrations in 338 subjects (149 healthy subjects, 115 patients with T1D, and 74 patients with T2D) from 8 trials. The Applicant used a step-wise approach to develop the meta population PK model. Data from the different studies were added sequentially, ranked according to information content. The PK of insulin lispro following IV and SC administration of LYUMJEV and SC administration of Humalog in patients with T1D or T2D and healthy subjects was best characterized by a three-compartment model with linear elimination, and a mixed zero-order absorption and first-order absorption via transit compartments.

The pharmacometric reviewer determined that the Applicant’s population PK model appears adequate to describe the observed serum insulin lispro concentration-time profile following IV and SC LYUMJEV or SC Humalog administration in healthy subjects and patients with T1D or T2D. Therefore, the PK model is acceptable to simulate serum insulin lispro concentrations for exposure-response (E-R) analyses for efficacy and safety measurements. The Applicant conducted E-R analyses separately for T1D and T2D to quantify the relationship between insulin lispro concentration and postprandial glucose response following SC administration of LYUMJEV and Humalog when both insulins are given prior to the start of the meal and 20 minutes after the start of the meal.

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The pharmacometric reviewer concluded that the Applicant's simulation demonstrated a similar PPG excursion for when LYUMJEV is dosed 20 minutes post meal to when Humalog is dosed immediately before the start of the meal, which supports the proposed administration of LYUMJEV within 20 minutes after starting a meal in patients with T2D from the efficacy perspective. The Applicant's simulation also demonstrated low incidence of all documented hypoglycemia with BG $\leq$ 70 mg/dL or BG $\leq$ 54 mg/dL at various time periods for LYUMJEV post meal, which supports the proposed administration of LYUMJEV within 20 minutes after starting a meal in patients with T2D from the safety perspective.

In summary, the Applicant's modified integrated glucose-insulin (IGI) model developed for patients with T2D based on Phase 1 Trial ITRW, well predicted lower PPG excursion and generally similar incidences of all documented hypoglycemia for LYUMJEV compared to Humalog as observed in Phase 3 Trial ITRN when both insulins were given prior to the start of a meal. The model also predicted generally comparable PPG excursion and incidences of all documented hypoglycemia in patients with T2D for LYUMJEV administered 20 minutes postmeal compared to Humalog premeal, which supports the proposed administration of LYUMJEV within 20 minutes after starting a meal in patients with T2D.

Reviewer comment: See **Section 7.3 (Integrated Review of Effectiveness)** for the clinical assessment of the data supporting postmeal dosing of LY900014 in patients with T2D.

4.5.1. Mechanism of Action

The primary activity of insulin is the regulation of glucose metabolism. Insulin lispro, a human insulin analogue, exerts its specific action through binding to insulin receptors and stimulating tyrosine kinase activity, promoting receptor autophosphorylation and subsequent intracellular signaling. This event initiates a cascade of intracellular reactions leading to a number of metabolic and mitogenic effects including the translocation of glucose transporters to the cell surface, promoting glucose uptake. In addition, insulin receptor activation promotes lipid, protein, and glycogen synthesis and inhibits lipolysis, proteolysis, and gluconeogenesis.

4.5.2. Pharmacodynamics

Glucodynamics

Euglycemic clamp

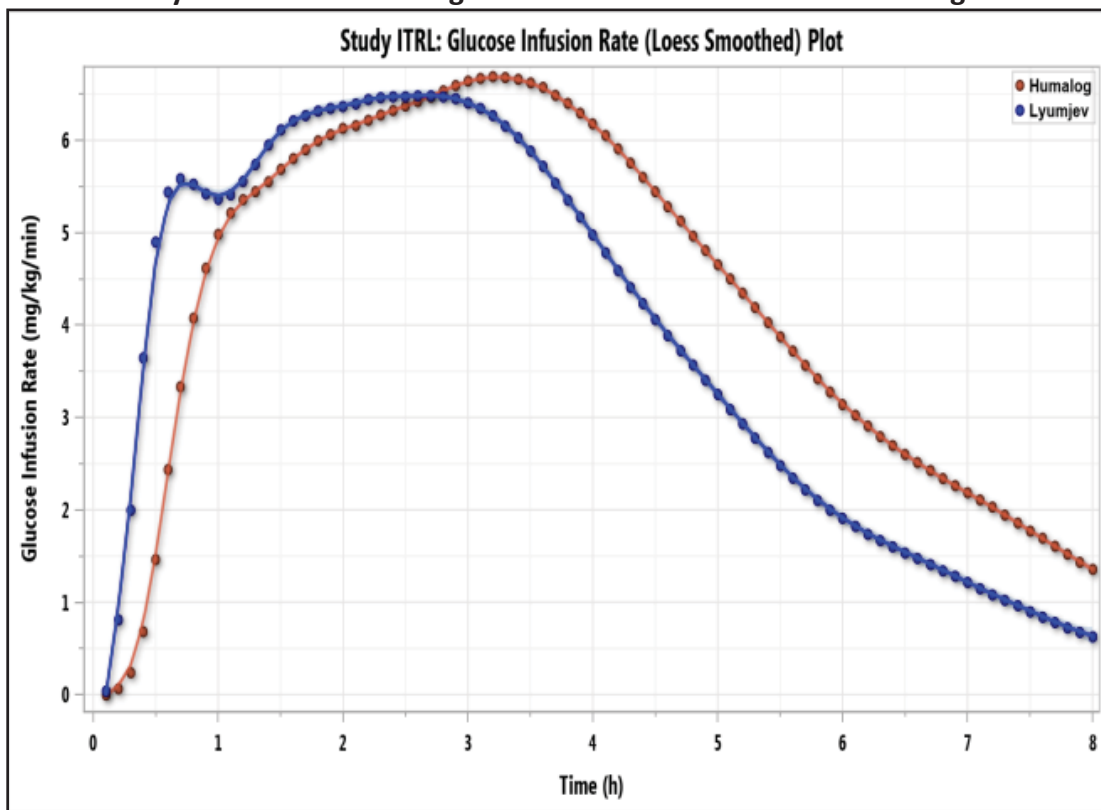
Study ITRL compared the PK and GD of insulin lispro following a single, 15 U SC dose of LYUMJEV with the PK and GD of a single, 15 U SC dose of Humalog. This was a Phase 1, single center, randomized, subject- and investigator-blind, 2-treatment, 2-period, crossover study in healthy subjects.

A slightly greater insulin onset of action within the first hour after dose administration was observed following LYUMJEV administration compared to Humalog (**Figure 1**). There were

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corresponding 13.8- and 2.21-fold increases in the $G_{\text{tot}(0-30\text{min})}$ and $G_{\text{tot}(0-1\text{h})}$, respectively, following LYUMJEV compared to Humalog (**Table 2**). There was a 41% reduction in time to onset of insulin action (T_{onset}) and 47% reduction in early 50% time to maximum glucose infusion rate ($t_{R_{\text{max}}}$) after LYUMJEV administration compared to Humalog (**Table 2**). A slightly lower G_{tot} was observed following LYUMJEV compared to Humalog. There was no statistically significant difference between treatments in R_{max} (**Table 2**).

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



Source: Excerpted from Clinical Pharmacology Review BLA 761109 page 18

Table 2: Pharmacodynamic Parameters and Statistical Analysis after Administration of 15 U of LYUMJEV Compared to 15 U Humalog

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

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	-13.88	(-15.85, -11.90)	<.0001	0.59	(0.55, 0.63)
	15 U LY900014	32	20.10					
tRmax (min)	15 U Humalog	32	170.81	-39.56	(-62.70, -16.43)	0.0069	0.77	(0.66, 0.90)
	15 U LY900014	32	131.25					
early 50% tmax (min)	15 U Humalog	32	55.07	-25.75	(-33.20, -18.29)	<.0001	0.53	(0.45, 0.63)
	15 U LY900014	32	29.33					
late 50% tmax (min)	15 U Humalog	31	335.84	-62.18	(-77.73, -46.62)	<.0001	0.81	(0.76, 0.87)
	15 U LY900014	32	273.67					

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: Excerpted from Clinical Pharmacology review page 27

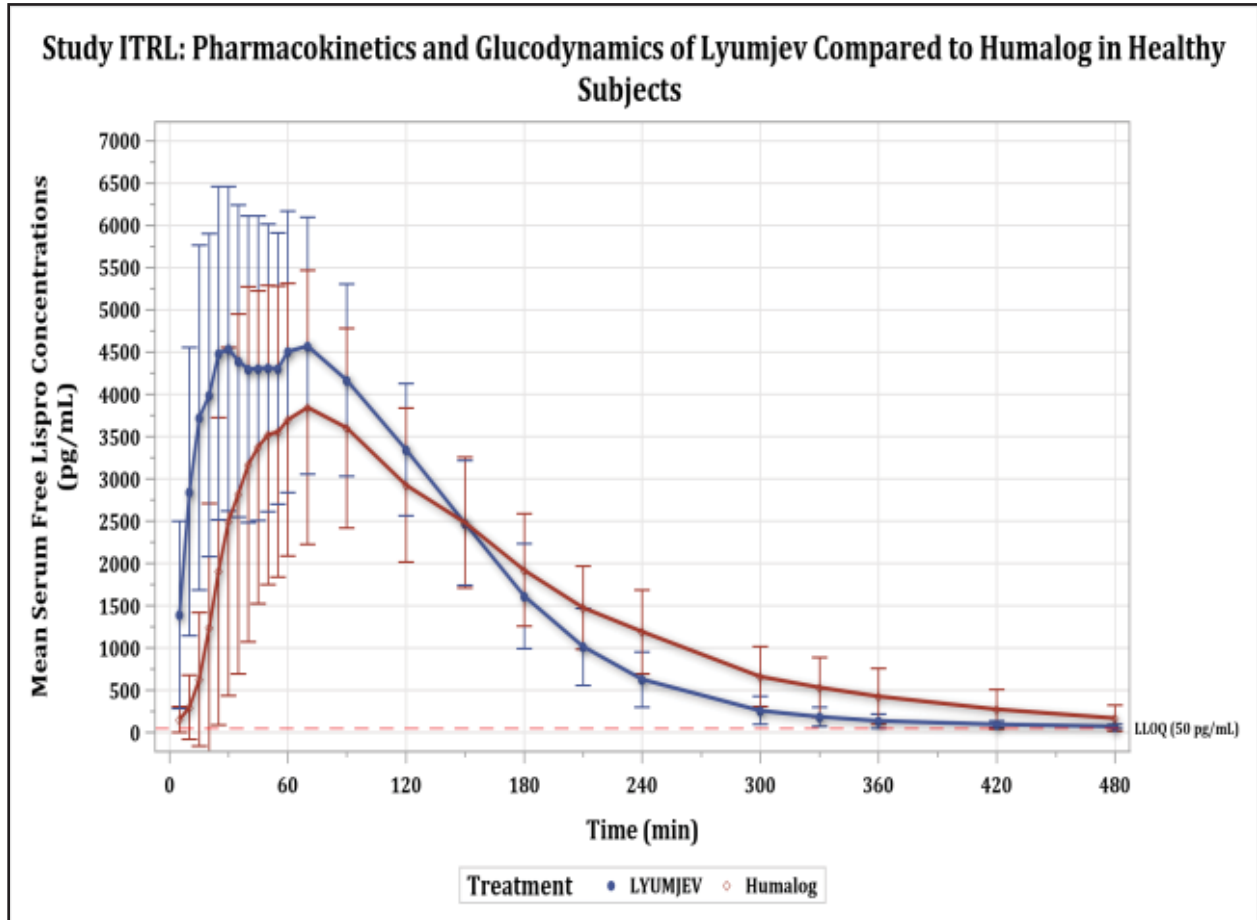
4.5.3. Pharmacokinetics

Euglycemic clamp

In Study ITRL, following administration of 15 U LYUMJEV or HUMALOG, faster, earlier insulin lispro absorption was seen for LYUMJEV compared to Humalog as seen by statistically significant changes in the early 50% T_{max} , $AUC_{(0-30min)}$, and $AUC_{(0-1h)}$ (**Figure 2 , Table 3**). Early 50% T_{max} for insulin lispro was reduced from 30.7 minutes to 10.8 minutes (~65%) following LYUMJEV administration compared to Humalog (**Table 3**). There were corresponding increases in $AUC_{(0-30min)}$ and $AUC_{(0-1h)}$ by approximately 4.61- and 1.99-fold, respectively, and a significantly higher C_{max} after LYUMJEV administration compared to Humalog (**Table 3**). There was a 46.5-minute mean (~24%) reduction in late 50% T_{max} for LYUMJEV compared to Humalog (**Table 3**). There was a corresponding 31% late insulin lispro exposure $AUC_{(2-8h)}$ reduction for LYUMJEV compared to Humalog (**Table 3**). However, the overall insulin exposure $AUC_{(0-\infty)}$ was not significantly different between LYUMJEV and Humalog (**Table 3**).

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Figure 2: Mean Insulin Lispro Concentration ($\pm$ SD) Versus Time by Treatment following 15 U doses of LYUMJEV and Humalog for Study ITRL



Source: Excerpted from Clinical Pharmacology Review BLA 761109 page 18

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Table 3: Statistical Analysis of the Pharmacokinetic Parameters of Insulin Lispro after Administration of 15 U of LYUMJEV Compared to 15 U of Humalog

Parameter	Treatment	N	Geometric Least squares means	Ratio of geometric least squares means Test : Reference	90% CI for the ratio (Lower, Upper)	P-value
C _{max} (pmol/L)	15 U Humalog	32	692	1.28	(1.17, 1.39)	<.0001
	15 U LY900014	30	893			
AUC(0-inf) (pmol.h/L)	15 U Humalog	32	1989	1.03	(0.986, 1.08)	0.2494
	15 U LY900014	31	2055			

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)
early 50% t _{max} (min)	15 U Humalog	32	30.7	-19.9	(-22.4, -17.4)	<.0001	0.352	(0.312, 0.395)
	15 U LY900014	30	10.8					
t _{max} (h)	15 U Humalog	32	1.34	-0.188	(-0.367, -0.010)	0.0832	0.848	(0.722, 0.988)
	15 U LY900014	31	1.06					
late 50% t _{max} (min)	15 U Humalog	32	197	-46.5	(-61.7, -31.3)	<.0001	0.765	(0.711, 0.826)
	15 U LY900014	31	151					
t _{1/2} (h)	15 U Humalog	32	1.16	-0.240	(-0.386, -0.093)	0.0093	0.794	(0.697, 0.909)
	15 U LY900014	31	0.921					

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

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

Source: Excerpted from Clinical Pharmacology Review BLA 761109 page 26

Table 4 provides a summary of the clinical pharmacokinetics of LY900014 (excerpted from the Clinical Pharmacology Review).

Table 4: Summary of Clinical Pharmacokinetics of LYUMJEV

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 (V_z) 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: excerpted from Clinical Pharmacology Review BLA 761109 page 11

Reviewer comment: In summary, results of the PK/PD studies reveal a faster time-action profile for LY900014 compared to Humalog. LY900014 compared to Humalog showed a more rapid onset of action for insulin lispro (~10 minutes faster), similar exposure, and shorter duration of action (~44 minutes shorter).

4.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) was consulted to evaluate the device performance and biocompatibility of the pen-injector submitted by the Applicant. The pen-injector proposed for use with LY900014 is a mechanical device based on the Applicant’s FDA approved KwikPen platform, and it is designed to deliver multiple doses of variable volume. The Applicant is proposing a set of four pen-injectors for the subcutaneous injection of LY900014 in two different drug strengths, with the following presentations: 100 U/mL Pen-Injector, 1 unit dose increments; 100 U/mL Junior Pen-Injector, 0.5 unit dose increments; 100 U/mL Tempo Pen-Injector, 1 unit dose increments; 200 U/mL Pen-Injector, 1 unit dose increments. The Tempo Pen differs from the other pen-injectors using the KwikPen platform (b) (4)

the use of the Tempo Pen with an external data transfer module, which enables the transfer

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insulin dosing information from the Tempo pen to a mobile medical application, thereby automating the creation of a dose collection diary. In the review of the device constituent component of this BLA, the CDRH reviewer, David Wolloscheck, PhD, determined all four presentations of LY900014 drug-device combination products approvable. For additional details, see Dr. Wolloscheck's review dated 4/16/2020.

4.7. Consumer Study Reviews

DMEPA was consulted to evaluate the human factors (HF) differentiation study results and labels and labeling submitted for Lyumjev (insulin lispro-aabc) Pre-filled Pen Injector (PPI), 100 units/mL and 200 units/mL for areas of vulnerability which may increase the risk for medication errors. The Applicant's HF differentiation study included 66 participants including pediatric patients and lay users, adult patients and lay caregivers, nurses, retail pharmacists and colorblind consumers. The study sought to demonstrate that the Lyumjev pre-filled pens can be differentiated from other products that users may take concurrently. After reviewing the participants' subjective feedback and the Applicant's root cause analyses in the six instances of selection error that occurred in the study, the DMEPA review concluded that none of the selection errors were attributed to aspects of the user interface; therefore, no changes to the user interface are needed. The evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors, and DMEPA has provided recommendations to be conveyed to the Applicant prior to BLA approval. DMEPA has determined that the recommended changes may be implemented without additional validation testing. For additional details, see Labels and Labeling and Human Factors Results Review by Janine Purcell, MS and Ariane Conrad, PharmD dated 5/7/2020.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical development program for this BLA included 18 clinical pharmacology trials and 3 phase 3 trials comprised of two multiple daily injection (MDI) studies and one CSII study. The clinical efficacy and safety studies submitted with this BLA are summarized in **Table 5**.

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Table 5: 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						
18B-MC-ITRM (PRONTO-T1D) Initiation date: July 17, 2017 Completion dates: September 6, 2018 (26 week) March 6, 2019 (52 week)	Trial Design: Phase 3, prospective, randomized, treat-to-target, multinational, 3-treatment group, parallel, active-controlled study in adults with T1D. 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 <u>Basal Insulin During Study:</u> - Insulin glargine 100 units/mL dosed SC once or twice daily; - Insulin degludec 100 units/mL dosed SC once daily	Primary endpoint: HbA1c at 26 weeks change in baseline Primary Objective (ITRM, ITRN): The primary objective of this study was to test the hypothesis that LY900014 was noninferior to Humalog on glycemic control (non-inferiority margin [NIM] = 0.4% for HbA1c) in patients with T1D (ITRM) and T2D (ITRN), when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec for 26 weeks.	26-week treatment period (open-label treatment) with 26-week primary endpoint 52-week treatment period (double-blind treatments) with 26-week primary endpoint 1-week screening, 8-week lead-in, 4- week safety follow-up, 26-week follow-up as needed for patients with treatment-emergent insulin lispro antibodies not returned to baseline.	Randomized/Safety Population: <u>LY900014:</u> 451 <u>Humalog:</u> 442 <u>LY+20:</u> 329	T1D for ≥1 year age ≥18 years using insulin ≥ 1 year continuously MDI ≥ 90 days including a rapid acting insulin analog HbA1c ≥7% to ≤9.5% BMI ≤ 35.0kg/m2	166 centers in 18 countries: U.S. Argentina Australia Austria Germany Greece India Italy Japan Mexico New Zealand Poland Romania Russia Slovakia Spain Sweden Taiwan
18B-MC-ITRN (PRONTO-T2D) Initiation date: July 14, 2017	Trial Design: Phase 3, prospective, randomized, treat-to-target, multinational, 2-treatment group, parallel, active-controlled study in adults with T2D. 2 Double-Blind Treatment Groups: Mealtime: LY900014 or Humalog	Primary endpoint: HbA1c at 26 weeks change in baseline Primary Objective (ITRM, ITRN): The primary objective of this study was to test the hypothesis that LY900014 was	26-week treatment period 1-week screening, 8-week lead-in, 4-week safety follow-up, 26-week follow-up for patients with treatment-emergent anti-lispro	Randomized/Safety Population: <u>LY900014:</u> 336 <u>Humalog:</u> 337	T2D for ≥1 year age ≥18 years MDI ≥ 90 days (basal insulin in combination with at least one	131 centers in 15 countries: U.S. Argentina Australia Czech-Republic

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Completion date: August 14, 2018	dosed SC 0-2 minutes prior to start of each meal. <u>Basal Insulin During Study:</u> - Insulin glargine 100 units/mL dosed SC once or twice daily; - Insulin degludec 100 units/mL or 200 units/mL dosed SC once daily <u>OAMs During Study:</u> Metformin and/or SGLT2 could be continued.	noninferior to Humalog on glycemic control (non-inferiority margin [NIM] = 0.4% for HbA1c) in patients with T1D (ITRM) and T2D (ITRN), when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec for 26 weeks.	antibodies not returned to baseline.		prandial injection or pre-mixed insulin injected at least twice daily) HbA1c ≥7% to ≤10% prior therapy allowed with up to 3 OAMs with stable dose BMI ≤ 45.0 kg/m²	Germany Hungary India Italy Japan South Korea Mexico Russia Slovakia Spain Taiwan
- Studies to Support Safety						
I8B-MC-ITSI (PRONTO-Pump) Initiation date: February 21, 2018 Completion date: September 4, 2018	Trial Design: Phase 3, prospective, randomized, double-blind, multinational, outpatient, 2-treatment group, crossover, active-controlled study in adults with T1D. 2 Double-Blind Treatment Groups: SCII administration of LY900014 and Humalog with meal bolus doses delivered 0-2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.	Primary endpoint: Rate (events/patient/30 days) of infusion set failures that lead to premature infusion set changes due to a pump occlusion alarm OR unexplained hyperglycemia with (e >250 mg/dL) that did not decrease within 1 hour following a correction bolus delivered via the pump.	Two 6-week treatment periods (no washout between periods). 1-week screening period, 2-week lead-in period 2-period crossover and a 4-week safety follow-up.	Randomized: <u>LY900014/ Humalog:</u> 24 <u>Humalog/ LY900014:</u> 25 Safety Population: <u>LY900014:</u> 49 <u>Humalog:</u> 48	T1D for ≥1 year on insulin therapy age ≥18 years using a rapid acting insulin analog via SCII for ≥6 months	5 study centers in 2 countries: U.S. Spain

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5.2. Review Strategy

The pivotal studies for this application are the two Phase 3 studies, Studies ITRM and ITRN. Study ITRM evaluated MDI administration of LY900014 versus Humalog in patients with T1D while Study ITRN enrolled patients with T2D. The study design and details of ITRM and ITRN are discussed in the review of relevant individual trials to support efficacy in **Section 6.1.1** and **Section 6.2.1**, respectively. Data from Study ITSI were submitted to provide additional exposure and supportive safety information. While efficacy data from Study ITSI are included in the ITSI Clinical Study Report (CSR), these results are not presented in the discussion of efficacy as the Applicant is not seeking an indication for CSII administration with this BLA submission.

The analyses used to formulate my conclusions of efficacy and determine the data to be included in labeling are the analyses which were conducted and/or corroborated by the FDA statistical reviewer, Dr. Anna Kettermann. The Applicant's original analyses were found to be discordant with the FDA results. The Applicant-defined Intent to Treat (ITT) population included all randomized subjects who had at least one baseline and one post-baseline value. The FDA analyses included all subjects who had a baseline assessment, including subjects who did not have a post-baseline assessment. A return to baseline multiple imputation approach was used to impute missing data. The Applicant reanalyzed the data for the primary endpoints using the Agency's preferred estimand of all randomized subjects, irrespective of the presence of post-baseline data. The reanalyzed data were resubmitted, Dr. Kettermann reviewed and concurred with the results, and these results were incorporated into the Applicant's proposed label. My review primarily discusses results of analyses conducted by Dr. Kettermann and includes my evaluation of the Applicant's results as supportive information. For a detailed discussion of the statistical analyses of the trial, please refer to the Statistical Review by Dr. Kettermann, dated 4/15/2020. Refer to **Section 8** for safety review approach.

While the efficacy results are discussed individually, since Studies ITRM and ITRN have similar designs and endpoints, some of the data in **Section 6**, including tables summarizing details of the protocol and efficacy findings, present similar information and are therefore cross referenced during my review. The primary and multiplicity adjusted secondary endpoints are mainly discussed in **Section 6**. 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 hypoglycemia are discussed under submission specific safety issues in **Section 8.5.1**. Other secondary endpoints such as self-monitored blood glucose (SMBG) profiles, glycemic variability, and 1,5-anhydroglucitol are considered exploratory and are not further discussed in this review. A brief discussion of the primary endpoints of the CGM sub-study, (b) (4) is also included.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study ITRM

Study title: A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro with an Open-Label Postprandial LY900014 Treatment Group, in Combination with Insulin Glargine or Insulin Degludec, in Adults with Type 1 Diabetes PRONTO-T1D

6.1.1. Study Design

Overview and Objectives

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.

Multiplicity-adjusted objectives included demonstrating that LY900014 was:

- superior to Humalog in controlling 1-hour and 2-hour PPG excursions MMTT at Week 26 when administered as prandial insulin;
- superior to Humalog on glycemic control as measured by change from baseline to Week 26 in HbA1c when administered as prandial insulin;
- noninferior to Humalog on glycemic control as measured by change from baseline to Week 26 in HbA1c (NIM= 0.4%) when administered 20 minutes after the start of a meal.

Investigational Product (IP)

Study insulins (LY900014 and Humalog) were supplied by Lilly or its representative, in accordance with current good manufacturing practices, and were supplied with clinical trial lot numbers. Instructions for Use for the prefilled devices were provided. The blinded prefilled pens contained a concentration of 100 U/mL in 3-mL cartridges of either LY900014 or Humalog. The open-label prefilled pens contained a concentration of 100 U/mL of LY900014. During the lead-in period, 100 U/mL Humalog was provided using open-label prefilled pens.

Trial Design (see **Figure 3** for Study Design and **Table 43** for Schedule of Assessments)

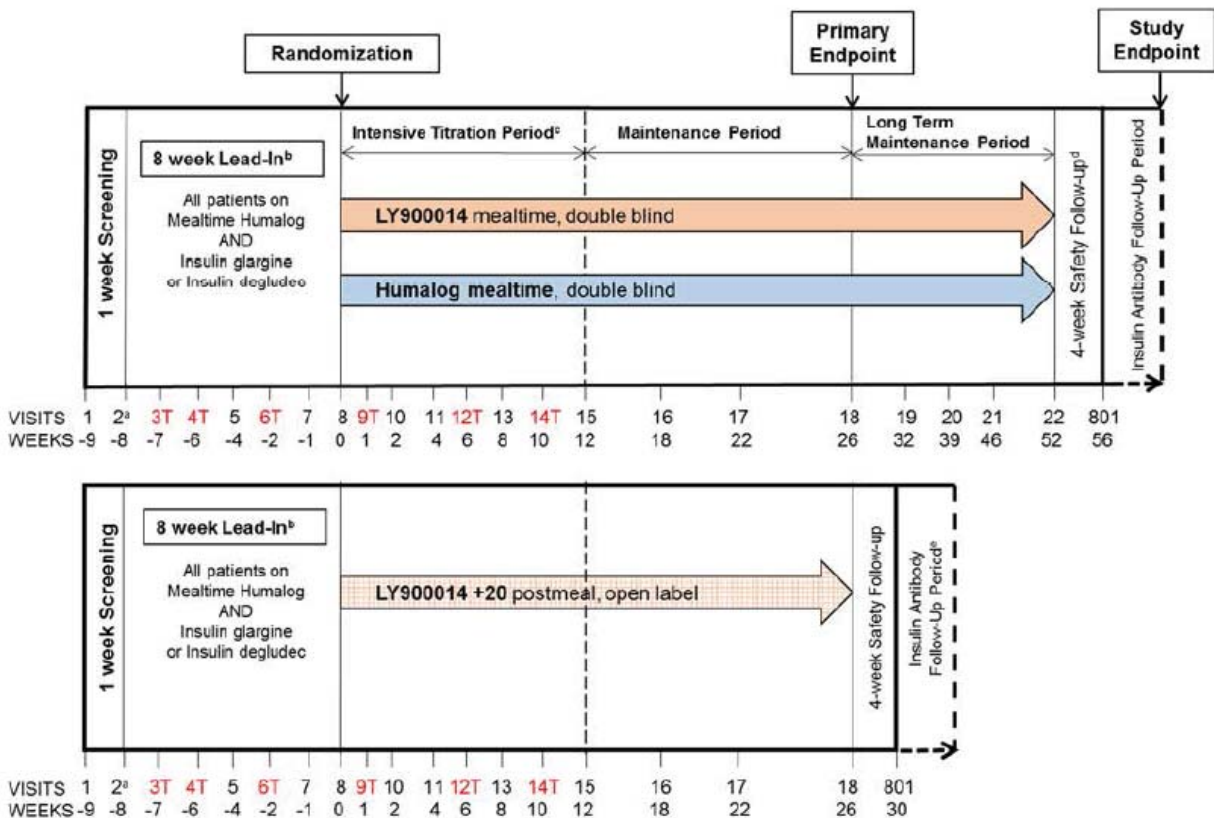
ITRM was a 52-week, Phase 3, prospective, randomized, multinational, 3-treatment arm, parallel, active-controlled study which compared treatment with LY900014 or Humalog in patients with T1D currently using an MDI regimen for at least 90 days. In 2 of the treatment groups, LY900014 and Humalog were administered immediately (0-2 minutes) prior to the start of the meal in a double-blind manner. A third open-label treatment group consisted of

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LY900014 administered 20 minutes after the start of a meal (LY+20).

Reviewer comment: The trial design for ITRM (and ITRN) and NIM of 0.4% were agreed upon at the EOP-2 meeting.

Figure 3: Study Design Protocol ITRM



Abbreviation: T = telephone visit.

a At Visit 2, patients on insulin glulisine or insulin aspart were transferred to Humalog. The patients' basal insulin regimen was switched to insulin glargine U-100 (once or twice daily) or to insulin degludec U-100 once daily. At Visit 8, patients were randomized to either premeal (0-2 minutes before the start of the meal) Humalog, premeal LY900014, or LY900014+20 and continued their basal insulin regimen.

b Titrate basal insulin.

c Titrate prandial insulin (Humalog or LY900014).

d Patients discontinued study insulins at Week 26 for the LY900014+20 open-label treatment group or will discontinue study insulins at Week 52 for the 2 blinded treatment groups and the LY900014 open-label treatment group in Japan.

e Eligible patients had visits at approximately 3-month intervals for up to 26 weeks after Visit 801 for follow-up of insulin lispro antibody levels.

Source: CSR ITRM Figure ITRM.9.1

Study Periods:

The study included a 1-week **screening period**, an 8-week **lead-in period**, followed by a 26-week (primary endpoint) or 52-week **treatment period**, and a 4-week **safety follow-up period**. All patients who completed the 4-week safety follow-up visit (Visit 801; Week 30 or Week 56) and had treatment-emergent insulin lispro antibodies (TEADA) that had not returned to the prespecified baseline range (Visit 2; Week -8) were asked to participate in follow-up to monitor

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anti-lispro antibody (ADA) levels for up to 26 weeks after Visit 801.

For treatment arms with mealtime dosing, LY900014 and Humalog were administered in a double-blind manner. Subjects in these groups completed a 52-week treatment period (with primary endpoint at 26 weeks). The double-blind treatment groups continued in the study for 52 weeks to provide additional safety and efficacy data. The LY+20 treatment arm was open-label, and this group completed a 26-week treatment period.

During the **lead-in period** (Week -8 to 0), all patients received nutritional counseling and were provided with a study glucose meter and monitoring supplies in order to perform SMBG testing, minimally with 4 readings daily. All patients were switched to Humalog insulin for prandial insulin. Patients on alternative basal insulin therapies were switched to insulin glargine U-100 once or twice daily, or insulin degludec U-100 once daily for basal insulin, as determined by the investigator, and remained on the same basal insulin regimen throughout the trial. The purpose of the lead-in period was to titrate basal insulin, obtain preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates.

At **randomization** (Week 0), subjects were randomized in a 4:4:3 ratio to either LY900014 at mealtime, Humalog at mealtime, or LY900014 +20. Randomization stratification factors included the following: country; HbA1c ($\leq 7.5\%$ or $> 7.5\%$) at end of lead-in period; basal insulin (glargine U-100 or degludec U-100) during lead-in; prandial insulin dosing plan (carbohydrate counting or pattern adjustment). Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web-response system (IWRS).

During the **intensive titration period** (Week 0 to 12), prandial insulin doses were adjusted as necessary to meet the target SMBG levels based on titration algorithms provided in the protocol. During the **maintenance period** (Week 12 to 26), the prandial insulin doses were adjusted only to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia. During the **long-term maintenance period** (Week 26 to 52), titration of prandial and basal insulin occurred in order to maintain or further optimize glycemic control.

The **safety follow-up period** occurred 4 weeks after IP discontinuation. Additional follow-up visits occurred for patients in whom TEADA levels had not returned to baseline levels and continued for up to 26 weeks after IP discontinuation.

Reviewer comment: *The 12-week lead-in period was adequate for washout of previously prescribed insulin products and for the titration and stabilization of basal insulin dose. The assessment of HbA1c as a baseline at the end of this period, prior to the beginning of 12-week intensive insulin titration period appears to be appropriate. Similarly, the 12-week period of intensive titration of prandial insulin, followed by 12-week maintenance period should provide ample time to assess the difference in treatment effect of LY900014 vs Humalog. Given the short*

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half-life of prandial insulin, the safety follow-up at 4 weeks after IP discontinuation is also acceptable.

Procedures and study schedule (See also **Table 43** for Schedule of Assessments):

The following activities occurred at the listed time points.

Review of concomitant medications, AEs, basal and prandial insulin dose assessments, 4-point SMBG profiles, hypoglycemia data:

- All visits

HbA1c assessment:

- Screening, Week -1, 0, 4, 8, 12, 26, 39, 52, or early discontinuation (ED) visit MMTT (4-hour) with a standardized 100 g carbohydrate liquid test meal with serum glucose measurements at time relative to start of meal (-15, 0, 15, 30, 60, 120, 180, 240 minutes):

- Week 0, 26

Body weight, vital signs assessment:

- Screening, weeks -8, -4, -1, 0, 2, 4, 8, 12, 18, 22, 26, 32, 39, 46, 52, 56, ED

Electrocardiogram (ECG), urinalysis, Follicle Stimulating Hormone assessment (females):

- Screening

Pregnancy testing:

- Screening, Week 0

Hematology, chemistry, lipid profile assessment:

- Screening, Week 0, 26, 52, ED

Nutritional counseling, diabetes counseling:

- Week -8

Titration of basal insulin:

- Week -8, -7, -6, -4, -2, -1

Titration of prandial insulin:

- Week 0, 1, 2, 4, 6, 8, 10, 12

Dispense IP:

- Week -8, -4, 0, 4, 8, 12, 18, 22, 26, 32, 39, 46

Anti-insulin lispro antibody assessment:

- Week -8, 0, 2, 4, 12, 26, 52, 56 (30), ED

Reviewer comment: *The timing of visits and the schedule of activities and planned assessments are appropriate for an insulin product.*

Trial locations:

The trial was conducted in 166 centers in the following 18 countries: US, Argentina, Australia, Austria, Germany, Greece, India, Italy, Japan, Mexico, New Zealand, Poland, Romania, Russia, Slovakia, Spain, Sweden, Taiwan.

Key inclusion criteria:

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- adults ≥ 18 years of age with T1D for at least 1 year at screening
- use of insulin continuously for at least 1 year at screening
- on MDI therapy with prandial insulin (lispro U-100, aspart, or glulisine) for at least 90 days
- on treatment with basal insulin (glargine U-100 or U-300; detemir U-100; degludec U-100 or U-200; or NPH) for at least 30 days
- body mass index (BMI) of ≤ 35.0 kg/m² at screening
- women of childbearing potential not pregnant, not breastfeeding, and sexually abstinent or using highly effective method of contraception
- HbA1c $\geq 7.0\%$ and $\leq 9.5\%$

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
- liver disease, renal transplant, or dialysis
- significant cardiac or gastrointestinal disease
- history of cancer within previous 5 years (exception of basal cell carcinoma)
- 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
- excessive insulin resistance at screening (total daily insulin dose >1.5 U/kg)
- chronic (> 14 consecutive days) systemic glucocorticoid therapy at pharmacological doses within 8 weeks preceding screening (exception of replacement therapy for adrenal insufficiency)
- treatment with regular human insulin or premixed insulins within 90 days prior to screening
- treatment with oral or injectable medication for the treatment of diabetes mellitus other than insulins in the 90 days prior to screening

Reviewer comment: *In general, the inclusion and exclusion criteria appear appropriate. The lower HbA1c threshold of 7.0% for inclusion in study participation may make the assessment of treatment effect more challenging in patients with values in this lower range. Risk to patients was appropriately minimized by the exclusion of participants with hypoglycemia unawareness and/or a 6-month history of clinically significant hyperglycemia and/or DKA.*

Insulin dosing, monitoring and titration:

Investigators used SMBG levels to make treatment decisions to achieve glycemic goals (see **Table 6**). While insulin titration algorithms were provided, modifications in the calculation of the patients' insulin doses may also have been influenced by other clinical circumstances and safety considerations known to the investigator. Thus, the prescribed insulin doses during the study were individualized, and were determined by and were the responsibility of the

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investigator.

Reviewer comment: *The flexibility given to the investigator for individualizing insulin dosing, while necessary for safety purposes, makes assessment of adherence to titration algorithm challenging. An information request to the Applicant sent from the statistical reviewer confirmed that site-prescribed insulin dose information was not collected for the Phase 3 studies. The review of efficacy includes a closer review of differences in insulin dosing between treatment arms in the trials.*

Basal insulin:

During the lead-in period (Week -8 to 0), the patients' basal insulin was titrated every 3 to 4 days as necessary using the titration algorithm to reach the FBG target of 100 mg/dL (see **Table 7**). Basal insulin dose was adjusted, if needed, to facilitate optimal prandial insulin dosing during the insulin intensive titration period (Weeks 0 to 12) or for safety reasons. Thereafter, during the maintenance period (Weeks 12 to 26), adjustments to basal insulin doses were made to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia. During the long-term maintenance period (Week 26 to 52), investigators, in discussion with patients, titrated prandial and/or basal insulin as needed in order to maintain or optimize glycemic control.

Prandial insulin:

This study used 2 possible plans for determining prandial insulin dosing:

- Pattern adjustment: a fixed dose or dose range of insulin for each meal, which may be individualized for each meal.
- Carbohydrate counting: a meal dose is calculated based on an estimate of the carbohydrate content of meal multiplied by insulin to carbohydrate ratio (ICR) as unit insulin per grams carbohydrate.

Patients maintained the same prandial insulin dosing plan throughout the study. Incorporation of a correction factor (e.g., 1 unit of insulin per glucose [mg/dL] above target goal) may also have been implemented with either prandial insulin dosing plan.

For patients who were carbohydrate counting, the ICR and correction factor were assessed and adjusted as needed, every 3-4 days, in order to meet the target SMBG (see **Table 6**) during the intensive titration period (Week 0 to 12). For patients who followed the pattern adjustment plan, the patients' prandial insulin was titrated every 3 to 4 days as necessary using the titration algorithm to reach glycemic goals (see **Table 8**). Thereafter, during the maintenance period (Week 12 to 26), adjustments to prandial insulin doses were made to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia. During the long-term maintenance period (Week 26 to 52), investigators, in discussion with patients, titrated prandial and/or basal insulin as needed in order to maintain or optimize glycemic control.

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Table 6: Target Glucose Values for Adjustment of Insulin Therapy¹

Time of Target Blood Glucose Measurement	Self-Monitored Blood Glucose (SMBG) Target (Range)
Fasting or pre morning meal	Target: 100 mg/dL Range: 80 to <110 mg/dL
Pre midday meal	Target: 100 mg/dL Range: 80 to <110 mg/dL
Pre evening meal	Target: 100 mg/dL Range: 80 to <110 mg/dL
Pre bedtime	Range: 90 to 130 mg/dL
1-2 hour postprandial	Target: <140 mg/dL

Source: CSR ITRM Table ITRM.9.2

Table 7: Basal Insulin Adjustments Algorithm for ITRM

If median (middle) FBG ^a from the 3 previous FBG values is:	<i>When Basal Insulin ≤14 units</i>	<i>When Basal Insulin ≥15 units</i>
	Adjust the basal dose by:	Adjust the basal dose by:
≤70 mg/dL	Decreasing dose to previous lower dose ^b	Decreasing dose to previous lower dose ^b
71–100 mg/dL	No adjustment	No adjustment
101–139 mg/dL	Increasing by 1 unit	Increasing by 2 units
140–179 mg/dL	Increasing by 2 units	Increasing by 3 units
≥180 mg/dL	Increasing by 3 units	Increasing by 4 units

Abbreviation: FBG = fasting blood glucose;

a: For patients using insulin glargine twice daily, investigators may also consider use of evening premeal SMBG values for assessment of morning insulin glargine dose.

b: If there is no previous dose because this was the first assigned dose after randomization, then the basal dose should be decreased by 10% in consultation with the investigator.

Source: Protocol ITRM Table ITRM.5.

¹ Bailey TS, Grunberger G, Bode BW, et al; American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE). American Association of Clinical Endocrinologists and American College of Endocrinology 2016 outpatient glucose monitoring consensus statement [published correction appears in *Endocr Pract.* 2016;22(4);516. <https://doi.org/10.4158/1934-2403-22.4.516>]. *Endocr Pract.* 2016;22(2):231-261. <https://doi.org/10.4158/EP151124.CS>

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Table 8: LY900014 or Insulin Lispro Adjustment Algorithm Pattern Adjustment Plan

If Meal Time Dose of Insulin Lispro is:	Median SMBG Value Below Target Range	Median SMBG Value at Target Range ^a	Median SMBG Value Above Target Range
<10 units	Decrease by 1 unit	No change	Increase by 1 unit
11–19 units	Decrease by 2 units	No change	Increase by 2 units
≥20 units	Decrease by 3 units	No change	Increase by 3 units

Abbreviation: SMBG = self-monitored blood glucose.

^a Median SMBG value at target range OR experienced 1 unexplained hypoglycemic event (≤ 70 mg/dL) or signs/symptoms consistent with hypoglycemia noted.

Target Range: Premeal: 80-130 mg/dL
Bedtime: 90-130 mg/dL
1-2 hour postprandial <140 mg/dL

Source: Protocol ITRM Table ITRM.7. (same as Table ITRN.7.)

Reviewer comment: *The glycemic goals are based on treatment guidelines recommended by the American Association of Clinical Endocrinologists and titration algorithms for both basal and prandial insulin appear to be appropriate. The stratification of pattern vs carbohydrate counting is also helpful, since patients selecting carbohydrate counting may have more day to day variability in the doses of insulin administered based on dietary choices. The use of a correction factor may influence the doses of insulin administered; however, in general, the amount of supplemental insulin given with the use of this dosing tool is relatively small and does not contribute any more to the difficulty in assessing differences in insulin dosing than the individualization of dosing.*

Subject completion, withdrawal, and discontinuation criteria:

Randomized patients who discontinued the IP prematurely were encouraged to remain in the study, without study drug, for continued monitoring. Patients were to be discontinued from the IP in the following circumstances if:

- they experienced an AE, SAE, or clinically significant laboratory value (at the discretion of the investigator)
- they decided to stop IP
- they became pregnant
- if unblinding of investigator, study personnel performing assessments, or patient occurred
- they required treatment with another therapeutic regimen (including a change to the prescribed basal insulin injection time for insulin glargine U-100) or therapeutic agent (including addition of a second basal insulin injection) that had been demonstrated to be effective for treatment of the study indication
- they received concomitant prohibited medication
- they were nonadherent to IP therapy for more than 14 consecutive days

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Discontinuation of the IP for abnormal liver tests was to be considered by the investigator when a patient met one of the following conditions after consultation with the Lilly designated medical monitor:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X the upper limit of normal (ULN)
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin (TBL) >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Reviewer comment: *The study withdrawal and discontinuation criteria are appropriate.*

Treatment compliance:

The investigator assessed compliance of the patient at each visit, based on a review of the patient's glycemic control, adherence to the visit and treatment schedule, and completion of patient electronic clinical outcomes assessment (eCOA). The eCOA diary wirelessly received all glucose data directly from the BG meters, thereby increasing the validity of measures reported by the patient and minimizing transcription errors in recording the measures. Patients who were deemed noncompliant were to receive additional diabetes education and training. Patients who, in the opinion of the investigator, were deemed consistently noncompliant may have been discontinued from IP or from the study. The prandial insulin dose times and meal times were to be collected for assessing compliance of the timing of prandial insulin administration relative to meal time (premeal and postmeal).

Study Endpoints

Primary endpoint:

Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c

Multiplicity adjusted endpoints:

- Difference between LY900014 and Humalog in the 1-hour PPG excursion (serum glucose measured 1 hour after the start of the meal minus fasting serum glucose) from a MMTT at Week 26
- Difference between LY900014 and Humalog in the 2-hour PPG excursion (serum glucose measured 2 hours after the start of the meal minus fasting serum glucose) from an MMTT at Week 26
- Difference between LY900014 and Humalog in change in HbA1c from baseline to Week 26
- Difference between LY+20 and Humalog in change in HbA1c from baseline to Week 26

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Safety endpoints:

- AEs were collected at every visit and recorded, regardless of relationship to study drug. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA).
- Concomitant therapies were recorded at every visit.
- Laboratory data, including chemistry, hematology, and urinalysis panels, were collected at regular intervals. A urine drug screen, thyroid function test, and pregnancy test, if applicable, were completed at baseline.
- ECG was collected at baseline.
- Vital Signs including blood pressure, pulse rate, weight, and height, were collected at regular intervals.
- Hypoglycemia data was collected at every visit. See additional details in **Section 8.3.2**.
- SAEs were collected after the patient had received IP. See additional details in **Section 8.3.2**.
- Immunogenicity data was collected. See additional details in **Section 8.4.10**.

Other secondary endpoints:

- 1,5-anhydroglucitol (1,5-AG) change from baseline at Week 26 and Week 52
- 10-point self-monitored blood glucose (SMBG) profiles
- total, basal, and prandial insulin dose at Week 26 and Week 52
- proportion of patients achieving HbA1c targets (<7% and ≤6.5%) at Week 26 and Week 52

Reviewer comment: *The endpoint is change in HbA1c from baseline to Week 26. HbA1c has been accepted by FDA as an established surrogate biomarker for assessing the efficacy of anti-hyperglycemic agents².*

Statistical Considerations

For purposes of analysis, the following populations were defined:

- Entered: All patients who gave informed consent.
- Enrolled: All patients who received at least 1 dose of open-label Humalog in the 8-week lead-in period.
- Randomized: All patients who were randomly assigned to study treatment at Visit 8. Treatment group was defined on the basis of the treatment the patients were assigned.
- Safety: All randomized patients who received at least 1 dose of the randomly assigned IP. Treatment group was defined on the basis of the treatment to which the patients were assigned.
- Completer: Patients included in the randomized population who completed Week 26 of

² Guidance for Industry – Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention <http://www.fda.gov/downloads/Drugs/Guidances/ucm071624.pdf>

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study treatment without permanent discontinuation of IP. Treatment group was defined on the basis of the treatment the patients were assigned.

- Per-protocol: Patients included in the randomized population who completed Week 26 of study treatment without permanent discontinuation of IP and without important protocol deviations through Week 26 that would significantly impact the primary objective. Treatment group was defined on the basis of the treatment the patients actually received.

Efficacy analyses were conducted on the randomized population and safety analyses were conducted on the safety population. Efficacy analyses were conducted on all randomized patients using an intention-to-treat (ITT) approach according to the treatment the patients were assigned. The analyses for the primary and multiplicity adjusted objectives were performed for the ITT estimand which included all data collected from randomization through Week 26, regardless of IP use.

The primary objective of this study (H1) was to test the hypothesis that LY900014 was noninferior to Humalog on glycemic control (NIM = 0.4% for HbA1c) in patients with T1D, when administered at mealtime, in combination with basal insulin for 26 weeks. LY900014 was declared noninferior to Humalog if the upper limit of the 2-sided 95% CI for the LS mean difference in the change from baseline in HbA1c for LY900014 and Humalog was below +0.4%.

The sample size for the study was determined based on the NIM of 0.4%. Assuming an NIM of 0.4%, no true difference between treatment arms, and an SD of 1.1%, approximately 371 completers in each double-blind treatment group provided at least 99% 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% CI (LY900014 – Humalog). Assuming a 15% dropout rate for 26 weeks, 4:4:3 randomization ratio (LY900014, Humalog, and LY+20), approximately 1199 patients needed to be randomized. This sample size also had 95% power to show noninferiority between LY900014 and Humalog using a 0.3% NIM at 26 weeks.

The applicant utilized “return to baseline” approach to impute missing data with pattern mixture model based on data from randomized subjects who had at least one post-baseline measurement. The missing HbA1c measurement at Week 26 was imputed by the patient-level observed baseline value plus a noise assuming a washout of any potential treatment effect. The noise followed a normal distribution with the variability estimated from the “washout HbA1c data,” which was derived by subtracting the corresponding treatment mean at Week 26 from individual no-missing HbA1c values at Week 26. After imputation, the primary efficacy comparison was based on the contrast between LY900014 and Humalog from an ANCOVA (ITT estimand). The model for the change from baseline to the Week 26 HbA1c endpoint included treatment and strata (pooled country, type of basal insulin, and prandial insulin dosing plan) as fixed effects and baseline HbA1c as a covariate.

A missing-not-at random- (MNAR-) based analysis for the ITT estimand, and a mixed-effect
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model repeated measures (MMRM) analysis using the per protocol and completer populations, were performed as a sensitivity analyses for the primary outcome. A graphical approach for multiple comparisons (Bretz et al. 2011) was used to strongly control the overall type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the multiplicity adjusted objectives.

Reviewer comment: *The NIM of 0.4% was agreed upon with the details of the design and statistical analysis plan discussed at the EOP-2 meeting. In her statistical review of the data submitted, Dr. Kettermann noted that the definition of ITT set used in the Applicant's analyses omitted subjects who did not have post-baseline data. Therefore, Dr. Kettermann reanalyzed the data in her review, also using return to baseline imputations for missing data, on **all** randomized subjects, regardless of availability of post-baseline data. Dr. Kettermann's analyses, which use the Agency's preferred definition of the ITT estimand and methodology handling missing data. The Applicant reanalyzed the primary endpoints and resubmitted their results, which Dr. Kettermann reviewed and corroborated. These results were incorporated into the proposed label and are discussed in my review.*

Protocol Amendments

The protocol was amended 6 times prior to enrollment of patients with minor revisions. The first protocol addendum involved the addition of a 14-day sub-study using continuous glucose monitoring (CGM) to evaluate the 24-hour glucose profile for LY900014 and Humalog in terms of incremental $AUC_{0-2\text{hours}}$ after meals, duration and percentage of time in optimum range, duration and percentage of time in hyper- and hypoglycemic ranges, and glucose variability. The remaining amendments were minor revisions in inclusion and exclusion criteria proposed to satisfy foreign regulatory agency requirements.

Reviewer comment: *In the EOP-2 meeting which reviewed Study ITRM, no discussion of CGM endpoints occurred;* (b) (4)

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has attested that studies were conducted in compliance with the International Conference on Harmonization 1996 Guideline for Good Clinical Practice, as well as all applicable laws and regulations.

Financial Disclosure

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In accordance with 21 CFR 54.4, the Applicant submitted Form 3454 for Study ITRM. The Applicant provided a list of investigators with disclosable financial interest which included two investigators, both from the United States, who had disclosed receiving honorariums: one accepted an honorarium of \$32,800 and enrolled 2 subjects; the other accepted an honorarium of \$37,558 and enrolled 14 subjects. See also **Section 13.2 Financial Disclosure** for additional details.

Based upon my review of the disclosable financial interests, I do not have concerns that these payments could have introduced bias to the study supporting this BLA. This study involved 663 investigators and 1222 study participants. Thus, less than 1% of the investigators had reportable financial interests and contributed less than 2% of randomized patients to Study ITRM. Additionally, this study was conducted as large multinational, multicentric, randomized clinical trial, which makes it less likely to be influenced by a small number of investigators.

Patient Disposition

Of the 1621 patients screened for Study ITRM, 1222 patients were randomized (Humalog =442; LY900014 =451; LY+20 =329). Randomized patients who discontinued IP use were encouraged to remain in the study. Overall, treatment discontinuation rates were low, with over 94% of patients completing 26 weeks of treatment. The reasons for discontinuation are summarized in **Table 9**.

Of the patients who discontinued the studies early during the treatment period, the most common reason for treatment discontinuation was withdrawal by subject. There were no statistically significant treatment differences in the treatment arms of the number of patients discontinuing treatment or in the reasons for treatment discontinuation. Of note, pregnancy was recorded as an AE leading to treatment discontinuation, and this was the only AE listed as reason for discontinuation in more than one patient. Only one patient was discontinued from each treatment arm for protocol deviation.

Additionally, approximately 92% of all patients in ITRM completed the 52-week study and study treatment with no statistically significant treatment differences in the proportion of patients who discontinued the study, study treatment, or the reasons for study or treatment discontinuation.

Table 9: Summary of Patients Continuing/Completing Study and Reasons for Discontinuation by Treatment Group at 26 Weeks Studies ITRM and ITRN: All Randomized Population

Patient Disposition	Study ITRM (T1D) MDI N=1222			Study ITRN (T2D) MDI N=673	
	Humalog N=442	LY900014 N=451	LY900014+20 N=329	Humalog N=337	LY900014 N=336
Continuing Study ^a	418 (94.6)	435 (96.5)	315 (95.7)	321 (95.3)	325 (96.7)
Study Discontinuation n (%)					
Discontinued	24 (5.4)	16 (3.5)	14 (4.3)	16 (4.7)	11 (3.3)
Adverse Event	1 (0.2)	3 (0.7)	2 (0.6)	1 (0.3)	0 (0.0)
Death	1 (0.2)	0	0	1 (0.3)	2 (0.6)
Lost to Follow-Up	3 (0.7)	0	1(0.3)	5 (1.5)	2 (0.6)
Other	2 (0.5)	1 (0.2)	0	0 (0.0)	2 (0.6)
Subject decision	16 (3.6)	11 (2.4)	11 (3.3)	9 (2.7)	5 (1.5)
Treatment Discontinuation n (%)					
Discontinued	28 (6.3)	22 (4.9)	19 (5.8)	18 (5.3)	19 (5.7)
Adverse Event ^b	4 (0.9)	6 (1.3)	5 (1.5)	3 (0.9)	4 (1.2)
Death	1 (0.2)	0	0	0 (0.0)	2 (0.6)
Lost to Follow-Up	3 (0.7)	0	0	4 (1.2)	1 (0.3)
Non-compliance with Study Drug	0	0	0	1 (0.3)	0 (0.0)
Other	2 (0.5)	1 (0.2)	0	1 (0.3)	2 (0.6)
Investigator Decision	0	0	1 (0.3)	0	0
Protocol Deviation	1 (0.2)	1 (0.2)	0	1 (0.3)	2 (0.6)
Subject decision	17 (3.8)	14 (3.1)	12 (3.6)	8 (2.4)	8 (2.4)

Abbreviations: MDI = multiple daily injections; N = number of patients in the analysis population; n = number of patients within the specified category; T1D = type 1 diabetes; T2D = type 2 diabetes.
a Study ITRM was ongoing at time of 26-week disposition assessment, n = patients continuing study
b Pregnancy was reported by 6 patients in Study ITRM and is included among the adverse event terms.
Source: Clinical Efficacy Summary Table 2.7.3.4

Demographic and Baseline Disease Characteristics (see Table 10)

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/m² 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%.

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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%.

Table 10: Summary of Demographic and Disease Characteristics Study ITRM

Parameter	Humalog (N=442)	LY900014 (N=451)	LY900014+20 (N=329)	Total (N=1222)	p-Value ^a
Sex, n (%)					
Female	186 (42.1)	201 (44.6)	147 (44.7)	534 (43.7)	0.692
Male	256 (57.9)	250 (55.4)	182 (55.3)	688 (56.3)	
Age (years)					
Mean (SD)	44.50 (13.62)	44.09 (13.71)	44.54 (14.26)	44.36 (13.82)	0.875
Minimum, Maximum	18, 78	18, 80	18, 84	18, 84	
Age Group, n (%)					
<65 years	407 (92.1)	415 (92.0)	302 (91.8)	1124 (92.0)	0.989
≥65 years	35 (7.9)	36 (8.0)	27 (8.2)	98 (8.0)	
Race, n (%)					
Asian	78 (17.6)	86 (19.1)	63 (19.1)	227 (18.6)	0.799
Black/African American	9 (2.0)	7 (1.6)	5 (1.5)	21 (1.7)	
White	344 (77.8)	346 (76.7)	254 (77.2)	944 (77.3)	
Ethnicity, n (%)					
Hispanic or Latino	33 (7.5)	35 (7.8)	35 (10.6)	103 (8.4)	0.447
Not Hispanic or Latino	397 (89.8)	399 (88.5)	283 (86.0)	1079 (88.3)	
BMI (kg/m ²)					
Mean (SD)	26.39 (4.33)	26.61 (4.23)	26.68 (4.55)	26.55 (4.35)	0.626
Minimum, Maximum	17.10, 41.90	17.70, 40.00	15.50, 37.30	15.50, 41.90	
Duration of Diabetes (years)					
Mean (SD)	19.13 (12.04)	18.76 (12.26)	18.77 (11.70)	18.90 (12.02)	0.879
Minimum, Maximum	1.23, 59.23	1.07, 63.27	1.11, 64.18	1.07, 64.18	
HbA1c, Mean (SD)					
Screening (%)	8.02 (0.67)	8.04 (0.65)	8.03 (0.61)	8.03 (0.65)	0.880
Baseline (%)	7.33 (0.67)	7.34 (0.65)	7.36 (0.64)	7.34 (0.65)	0.840
FSG, Mean (SD)					
Study Entry (mg/dL)	176.05 (72.53)	171.61 (75.29)	175.00 (75.25)	174.13 (74.26)	0.654
Baseline (mg/dL)	126.19 (41.56)	126.29 (41.98)	129.51 (44.67)	127.11 (42.55)	0.507
Pre-study Bolus Insulin, n (%)					
Insulin Aspart	216 (48.9)	218 (48.3)	163 (49.5)	597 (48.9)	0.540
Insulin Glulisine	65 (14.7)	51 (11.3)	40 (12.2)	156 (12.8)	
Insulin Lispro	161 (36.4)	182 (40.4)	126 (38.3)	469 (38.4)	
Pre-study Basal Insulin, n (%)					

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Insulin glargine	262 (59.3)	257 (56.9)	187 (56.9)	706 (57.8)	0.938
NPH	8 (1.8)	12 (2.7)	9 (2.7)	29 (2.4)	
Insulin degludec	127 (28.7)	142 (31.5)	109 (33.1)	378 (30.9)	
Insulin detemir	45 (10.2)	40 (8.9)	24 (7.3)	109 (8.9)	
Lead-in Basal Insulin, n (%)					0.880
Insulin glargine	249 (56.3)	254 (56.3)	180 (54.7)	539 (44.1)	
Insulin degludec	193 (43.7)	197 (43.7)	149 (45.3)	683 (55.9)	
Region, n (%)					
United States	128 (29)	132 (29.3)	98 (29.8)	358	
Asia	78 (17.6)	83 (18.4)	62 (18.8)	223	
Europe	197 (44.6)	192 (42.6)	135 (41.0)	524	
South America	20 (4.5)	23 (5.1)	24 (7.3)	67	
Other	19 (4.3)	21 (4.7)	10 (3.0)	50	

Abbreviations: BMI = body mass index; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; N = total number of subjects in population; n = number of subjects; NPH = neutral protamine Hagedorn; SD = standard deviation. a p-Value for overall treatment effect.

Source: CSR ITRM Table ITRM.11.1

Reviewer comment: *Treatment arms were balanced in terms of age, race, ethnicity, BMI, and duration of T1D. Numerically, men were over-represented. In comparison to the US population, the demographic characteristics of study subjects under-represent African Americans and present a larger Asian subset. However, I do not think this racial imbalance had any effect on the outcome of the study or affects the generalizability of the results to the US population.*

Treatment Compliance

The prandial insulin dose times and meal times were recorded by patients for assessing compliance of the timing of prandial insulin administration relative to meal time (premeal and postmeal). Assessment of the compliance with injection timing relative to meals was compromised because of poor patient reporting of both meal and injection times, which represented approximately 45% of the study population. At the Week 26 morning meal, the proportions of patients with average dose times within the protocol-specified time window were as follows: LY900014, n=153 (86.9%); Humalog, n=138 (78.4%); LY+20, n=87 (69.0%). No patients were discontinued from treatment due to noncompliance with study drug by the investigator.

Reviewer comment: *Assessment of compliance in a regimen of four daily injections of insulin is challenging and was compromised in this study. The available data suggest that subjects in the LY+20 arm were less compliant, which is not surprising since dosing at fixed postmeal timepoint, when patients may be distracted leading to delay or forgetting to dose, may occur more often*

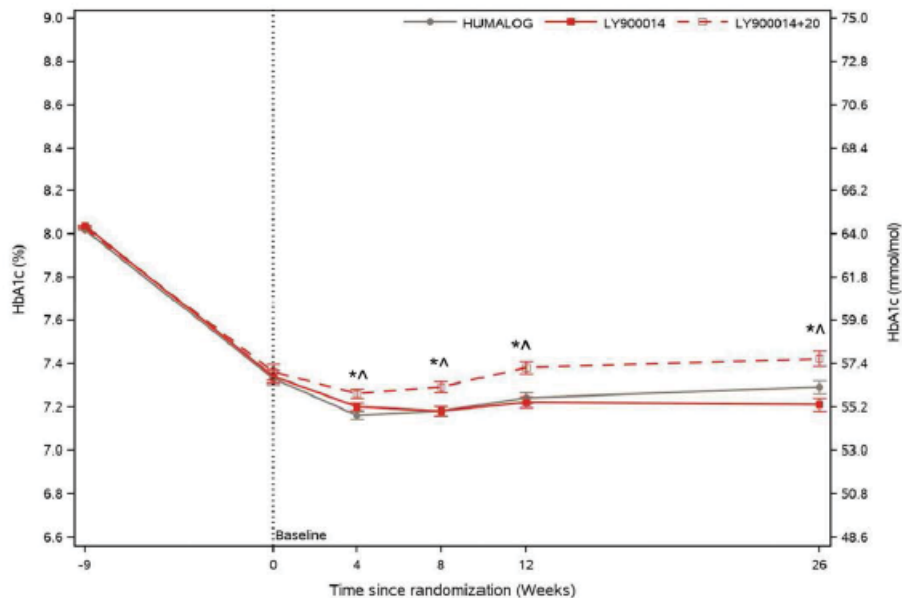
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than mealtime dosing. Lower compliance in the LY+20 treatment arm may have contributed to the smaller treatment effect noted.

Overview of Change in HbA1c During Study Periods

Figure 4 illustrates that similar changes in HbA1c occurred during the lead-in period (week -8 to 0) in all treatment arms. Modest additional reductions occurred the intensive titration period (week 0 to 12). Generally, HbA1c remained stable during the maintenance period (week 12 to 26) for the three treatment arms.

Figure 4: HbA1c from lead-in to Week 26 prior to discontinuation of IP



Source: CSR ITRM Figure ITRM.11.1

Table 11 provides a summary of the change in HbA1c from baseline to Week 26 for all treatment arms.

Table 11: HbA1c Actual and Change from Baseline in Studies ITRM and ITRN ITT Estimand

Treatment Group	HbA1c, LSM (SE)		
	Baseline	Week 26	Change from Baseline at Week 26
ITRM^{a,c}, HbA1c (%)			
Humalog	7.33 (0.03)	7.25 (0.04)	-0.09 (0.04)
LY900014	7.34 (0.03)	7.16 (0.04)	-0.18 (0.04)
LY900014+20	7.36 (0.04)	7.38 (0.04)	0.05 (0.04)
ITRN^{b,c}, HbA1c(%)			
Humalog	7.31 (0.04)	6.83 (0.05)	-0.46 (0.05)
LY900014	7.28 (0.04)	6.86 (0.05)	-0.43 (0.05)

Abbreviations: CI=confidence interval; HbA1c =hemoglobin A1c; LSM least-squares mean; SE =standard error.

Note: Number of randomized subjects:

Study ITRM: Humalog, N=442; LY900014, N=451; LY900014+20, N=329

Study ITRN: Humalog, N=337; LY900014, N=336

a Subjects included in the analysis are a subset of the randomized population that had baseline and at least one post-baseline assessment. The primary analysis included 450, 442, and 325 subjects randomized to and treated with mealtime LY900014, mealtime Humalog, and postmeal LY900014, respectively. Missing data at Week 26 were imputed by return to baseline, assuming a washout of any potential treatment effect. At Week 26, primary efficacy was missing for 3.6%, 4.8%, and 4% of subjects, for mealtime LY900014, mealtime Humalog, and postmeal LY900014, respectively.

b Subjects included in the analysis are a subset of the randomized population that had baseline and at least one post-baseline assessment. The primary analysis included 334 and 336 subjects randomized to and treated with mealtime LY900014 and mealtime Humalog, respectively. Missing data at Week 26 were imputed by return to baseline, assuming a washout of any potential treatment effect. At Week 26, primary efficacy was missing for 4.2% of subjects for both mealtime LY900014 and, mealtime Humalog.

c Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

Source: Modified from Clinical Summary of Efficacy Table 2.7.3.8.

Reviewer comment: It is notable from **Figure 4** and results in **Table 11** that most of the reduction in HbA1c occurred during the lead-in phase, when basal insulin was titrated. In addition to increases in basal insulin dose, patient enrollment into a clinical trial with early nutritional counseling, guided insulin titration, and regular visits with medical/study personnel likely resulted in better adherence to medication and diet contributing to the early decline in the HbA1c. HbA1c remained stable after insulin titration was completed, suggesting that patient compliance continued throughout the 26-week study.

Efficacy Results – Primary Endpoint

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The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. **Table 12** presents a summary of the FDA³ efficacy analysis for change in HbA1c from baseline for LY900014, LY+20, and Humalog. **Table 13** summarizes the FDA efficacy results of change in PPG excursion following MMTT between treatment arms. **Table 14** provides a summary of the Applicant’s primary and multiplicity adjusted efficacy results of change in PPG excursion following MMTT between treatment arms.

Table 12: Primary Analysis Outcomes Study ITRM with All Randomized Subjects

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 submitted by Applicant and corroborated by FDA Statistical Reviewer

³ The analyses were conducted using all randomized subjects, submitted by the Applicant, and corroborated by FDA Statistical reviewer.

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Table 13: MMTT PPG measurements at hour 1 and 2 Study ITRM

Treatment	Humalog N = 442	LY900014 N = 451	PPG hour
Baseline PPG excursion* Mean (std)	70.9 (62.85)	78.1 (60.43)	1
Change in PPG (95% CI)	0.25 (-4.88, 5.38)	-27.38 (-32.41, -22.34)	1
LY900014-Humalog (95% CI)	-27.63 (-34.83, -20.42)		1
Baseline PPG excursion* Mean (std)	99.1(89.55)	112.3(88.12)	2
Change in PPG (95% CI)	-1.62 (-8.72, 5.48)	-32.14 (-39.13, -25.16)	2
LY900014-Humalog (95% CI)	-30.52 (-40.50, -20.54)		2

*Results based on MMTT at the beginning of the trial

Source: Excerpted from Statistical Review BLA 761109

Table 14: Summary of Primary and Multiplicity Adjusted Efficacy Results for Study ITRM Using the Graphical Approach (ITT Estimand)

Hypothesis	Test	LSM (SE)		LY-Humalog LSM Difference (95% CI)	p-Value	NIM	Objective Met?
		Humalog	LY900014				
Primary Objective							
(H1) Change in HbA1c (%)	NI	-0.09 (0.04)	-0.18(0.04)	-0.08 (-0.161.-0.003)		0.4%, 0.3%	Yes
Multiplicity-Adjusted Secondary Objectives							
		Humalog	LY900014-20				
(H5) Change in HbA1c (%)	NI	-0.09 (0.04)	0.05 (0.04)	0.14(0.053.0.226)		0.4%, 0.3%	Yes
		Humalog	LY900014				
(H2) 1 hr PPG excursion (mg dL)	SP	74.3 (3.35)	46.7(3.34)	-27.6 (-35.0.-20.3)	<0.001		Yes
(H3) 2 hr PPG excursion (mg dL)	SP	103.8(4.51)	73.4(4.50)	-30.5 (-40.4. -20.6)	<0.001		Yes
(H4) Change in HbA1c (%)	SP	-0.09 (0.04)	-0.18(0.04)	-0.08 (-0.161.-0.003)	0.041		Yes

Abbreviations: CI = confidence interval; PPG = postprandial glucose; H = hypothesis; HbA1c = hemoglobin A1c; ITT = intent-to-treat; LSM = least-squares mean; NI = noninferiority comparison; NIM = noninferiority margin; SE = standard error; SP = superiority comparison;

Source: CSR ITRM modified from Table ITRM.11.2

(H1) 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.

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The upper limit of the 95% CI for the difference in change in HbA1c was also less than the noninferiority margin of 0.3%.

(H4) 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.

Reviewer comment: *The primary objective of the study of demonstrating noninferiority of mealtime LY900014 to Humalog on glycemic control was achieved. While statistically superior, the point estimate of the treatment difference (0.08) was small with an upper bound of the 95% confidence interval equal to zero. This trivial difference in HbA1c between treatments does not constitute a clinically relevant difference.*

Efficacy Results – Secondary and other relevant endpoints

(H5) 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%.

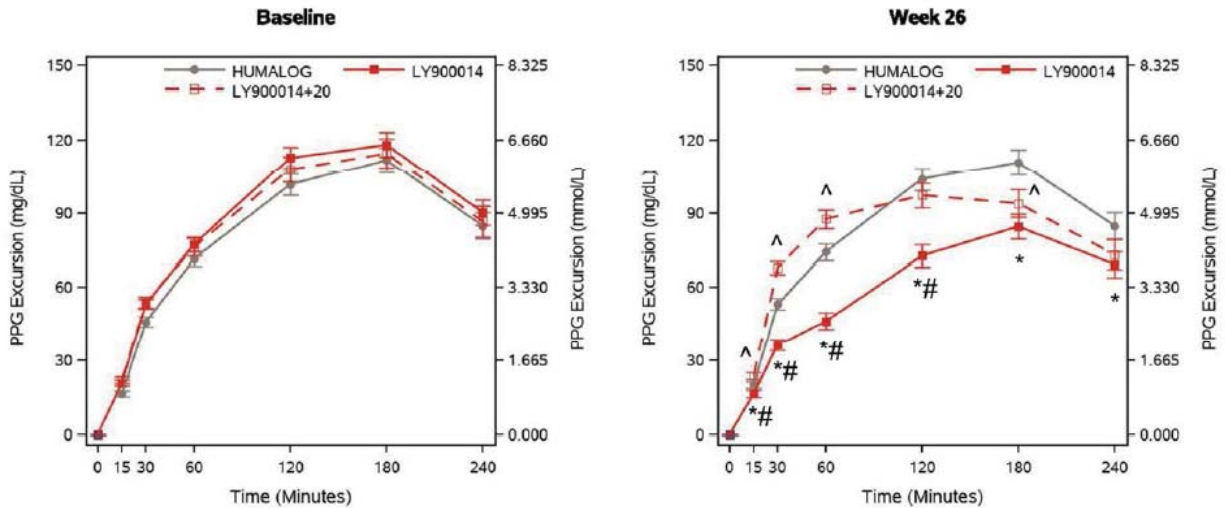
Reviewer comment: *While treatment with postmeal administration of LY900014 was confirmed to be noninferior to mealtime Humalog for HbA1c reduction in terms of the prespecified NIM, it should be noted that LY900014 +20 was statistically significantly inferior to Humalog (the treatment difference and the 95% CI was above zero for this comparison). Optimal timing for LY900014 is mealtime dosing.*

(H2) and (H3) 1-hour and 2-hour PPG excursions LY900014 vs Humalog: In both the Applicant and FDA analyses, LY900014 was superior to Humalog in controlling 1-hour and 2-hour PPG excursions during MMTT:

- 1-hour: LSM Difference (95% CI) = -27.63 mg/dl (-34.83, -20.42)
- 2-hour: LSM Difference (95% CI) = -30.52 mg/dl (-40.50, -20.54)

Reviewer comment: [REDACTED] (b) (4)
While results of MMTT revealed that PPG excursions were statistically significantly lower with LY900014 than Humalog, the clinical significance of this finding is not clear. The relative degree of PPG lowering that is clinically relevant has not been established [REDACTED] (b) (4)

Figure 5: Time course of blood glucose excursion during mixed-meal tolerance test from randomization to Week 26 prior to discontinuation of IP Study ITRM



Abbreviation: LSM = least squares mean; min = minutes; PPG = postprandial glucose; SE = standard error.

Data are LSM (SE)

*p<0.05 for pairwise comparison of LY900014 versus Humalog

^p<0.05 for pairwise comparison of LY900014+20 versus Humalog

#p<0.05 for pairwise comparison of LY900014+20 versus LY900014

Source: CSR ITRM Figure ITRM.11.2.

Reviewer comment: As demonstrated in **Figure 5**, PPG excursions following MMTT were statistically significantly lower with mealtime LY900014 treatment compared to Humalog treatment from all timepoints beginning at 15 minutes and continuing to 240 minutes. By comparison, PPG excursions at 15, 30 and 60 minutes were statistically significantly higher with LY+20 compared to Humalog, then similar to Humalog at other timepoints. PPG excursions were statistically significantly higher for LY+20 compared to LY900014 treatment until the 180-minute timepoint. Similar to HbA1c reduction, mealtime dosing of LY900014 demonstrates better efficacy than LY+20 for control of PPG excursion.

Proportions of Patients Achieving HbA1c Targets:

Overall, there were no significant treatment differences between the LY900014 and Humalog groups in the percentages of patients achieving HbA1c targets ($\leq 6.5\%$ and $< 7\%$) at Week 26. There were significantly fewer patients achieving these HbA1c targets in the LY+20 group than LY900014 and Humalog.

- $< 6.5\%$: Humalog, n= 70 (15.8%); LY900014, n=72 (16.0%); LY+20, n=31 (9.6%)
- $< 7\%$: Humalog, n= 150 (33.9%); LY900014, n=162 (36.0%); LY+20, n=80 (24.8%)

Reviewer comment: LY+20 treatment arm had fewer patients achieving target HbA1c goals and was statistically significantly inferior to Humalog in change in HbA1c. The data from the MMTT

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suggest that PPG is higher for the first 60 minutes with LY+20 dosing and later is similar to Humalog. These observations fit the time-action profile for LY900014. These findings also suggest that the lower treatment effect noted in terms of HbA1c reduction may have had more to do with lower compliance noted in the LY+20 arm.

Changes in Insulin Doses:

Since efficacy outcomes depend on optimal insulin dose titration, the average daily basal insulin dose, prandial insulin dose, total insulin dose, as well as the change from baseline in insulin doses were reviewed.

Table 15 presents a summary of basal, bolus, and total insulin dose at baseline and Week 26. **Figure 6** illustrates the mean daily basal, bolus, and total daily doses from baseline to Week 26.

- For basal insulin dose, there were no statistically significant treatment differences at baseline and Week 26 for insulin degludec and insulin glargine combined, or when basal insulins were analyzed separately.
- For prandial insulin dose, the only statistically significant difference between doses was that the dose of LY900014 was lower than LY+20 at baseline when adjusted for weight (LY900014, 0.39 U/kg; LY+20, 0.42 U/kg, $p=0.045$). There was no other statistically significant difference for bolus insulin at baseline or at Week 26.
- For total insulin dose, there were also no statistically significant treatment differences at baseline and Week 26 between treatment arms.

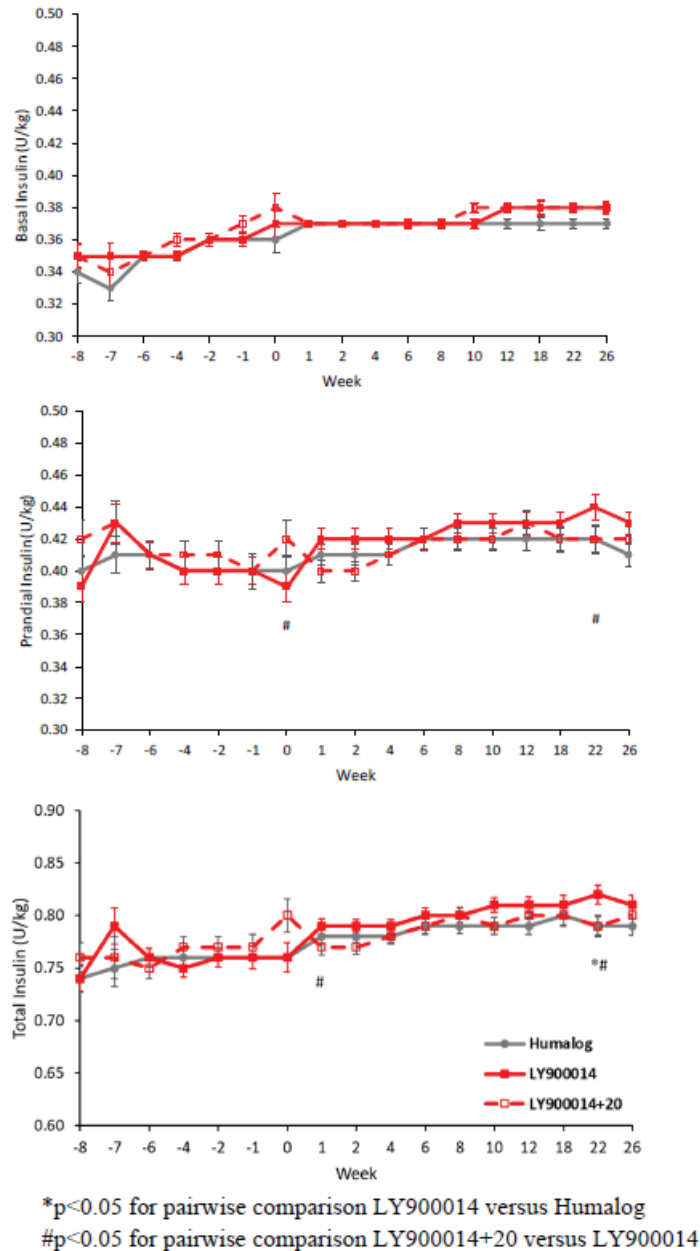
The daily mean insulin doses (basal, prandial, and total) in **Figure 6** illustrate that the titration pattern was similar in all treatment arms.

Table 15: Summary and Analysis of Insulin Dose (U/day and U/kg/day)

Timepoint	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	421	28.5 (0.78)	A: 1.0 (-1.1, 3.1), p=0.359	
		LY900014	434	29.5 (0.76)	B: 1.2 (-1.1, 3.5), p=0.316	
		LY900014+20	319	29.7 (0.89)	C: 0.2 (-2.1, 2.5), p=0.873	
	U/kg/day	Humalog	421	0.36 (0.01)	A: 0.01 (-0.01, 0.03), p=0.287	
		LY900014	434	0.37 (0.01)	B: 0.01 (-0.01, 0.04), p=0.254	
		LY900014+20	319	0.38 (0.01)	C: 0.00 (-0.02, 0.03), p=0.872	
Week 26	U/day	Humalog	371	29.9 (0.29)	A: 0.1 (-0.7, 0.8), p=0.846	
		LY900014	390	30.0 (0.28)	B: 0.3 (-0.5, 1.1), p=0.441	
		LY900014+20	283	30.2 (0.33)	C: 0.2 (-0.6, 1.1), p=0.550	
	U/kg/day	Humalog	371	0.37 (0.00)	A: 0.00 (-0.01, 0.01), p=0.597	
		LY900014	390	0.38 (0.00)	B: 0.01 (0.00, 0.02), p=0.305	
		LY900014+20	283	0.38 (0.00)	C: 0.00 (-0.01, 0.01), p=0.585	
Bolus						
Baseline	U/day	Humalog	433	31.4 (0.89)	A: -1.0 (-3.5, 1.4), p=0.410	
		LY900014	442	30.3 (0.88)	B: 1.5 (-1.1, 4.2), p=0.255	
		LY900014+20	325	32.9 (1.02)	C: 2.6 (-0.1, 5.2), p=0.057	
	U/kg/day	Humalog	433	0.40 (0.01)	A: -0.01 (-0.04, 0.02), p=0.525	
		LY900014	442	0.39 (0.01)	B: 0.02 (-0.01, 0.05), p=0.158	
		LY900014+20	325	0.42 (0.01)	C: 0.03 (0.00, 0.06), p=0.045	
Week 26	U/day	Humalog	379	32.5 (0.60)	A: 0.6 (-0.9, 2.1), p=0.455	
		LY900014	400	33.1 (0.59)	B: 0.0 (-1.6, 1.7), p=0.956	
		LY900014+20	285	32.6 (0.68)	C: -0.5 (-2.2, 1.1), p=0.526	
	U/kg/day	Humalog	379	0.41 (0.01)	A: 0.02 (0.00, 0.03), p=0.108	
		LY900014	400	0.43 (0.01)	B: 0.00 (-0.02, 0.02), p=0.705	
		LY900014+20	285	0.42 (0.01)	C: -0.01 (-0.03, 0.01), p=0.272	
Total						
Baseline	U/day	Humalog	418	60.0 (1.41)	A: -0.1 (-4.0, 3.7), p=0.950	
		LY900014	433	59.8 (1.38)	B: 3.0 (-1.2, 7.2), p=0.163	
		LY900014+20	316	62.9 (1.62)	C: 3.1 (-1.1, 7.3), p=0.144	
	U/kg/day	Humalog	418	0.76 (0.01)	A: 0.00 (-0.04, 0.04), p=0.972	
		LY900014	433	0.76 (0.01)	B: 0.04 (0.00, 0.08), p=0.069	
		LY900014+20	316	0.80 (0.02)	C: 0.04 (0.00, 0.08), p=0.072	
Week 26	U/day	Humalog	367	62.5 (0.73)	A: 0.9 (-0.9, 2.8), p=0.323	
		LY900014	388	63.4 (0.72)	B: 0.2 (-1.8, 2.3), p=0.832	
		LY900014+20	278	62.7 (0.83)	C: -0.7 (-2.7, 1.3), p=0.485	
	U/kg/day	Humalog	367	0.79 (0.01)	A: 0.02 (0.00, 0.04), p=0.071	
		LY900014	388	0.81 (0.01)	B: 0.01 (-0.02, 0.03), p=0.602	
		LY900014+20	278	0.80 (0.01)	C: -0.01 (-0.04, 0.01), p=0.253	

Abbreviations: CI = confidence interval; Diff = difference; LSM = least squares mean; n = number of subjects; SE = standard error. **Source: CSR Study ITRM Table ITRM.11.7.**

Figure 6: Mean Basal, Prandial, and Total Daily Insulin Doses (U/kg) over Time Study ITRM.



Source: Response to IR September 29, 2019

Reviewer comment: Review of the insulin dose data do not suggest any significant differences in dosage or titration patterns, indicating that the treatment arms were similarly optimized and maintained during the study periods. Overall, insulin dosages were fairly stable for the 12 weeks prior to the Week 26 HbA1c assessment. It is noted that from baseline to Week 26, basal insulin

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dose increased in all treatment arms; however, the dose of prandial insulin increased in the Humalog and LY900014 treatment arms, while the dose declined in the LY+20 arm. Thus, LY+20 treatment arm received less prandial insulin and accordingly demonstrated the smallest treatment effect on HbA1c.

Data Quality and Integrity

For the efficacy data submitted to this BLA submission, the statistical review team concluded the quality of the datasets and associated documentation (reviewer guide and define files) were acceptable and I concur with this assessment.

Dose/Dose Response

Dosing issues are discussed throughout the review.

Durability of Response/Persistence of Effect

No studies were specifically designed to evaluate tolerance of LY900014; however, insulin lispro has been shown to maintain efficacy over long periods of time in clinical practice. The data from the ITRM 52-week study show that LY900014 was effective up to 12 months. **Figure 7** illustrates that over the course of 52 weeks, in both the Humalog and LY900014 treatment groups, HbA1c similarly improved during the lead-in and intensive titration phase, remained stable during the maintenance period, and increased marginally during the long-term maintenance period. There were no statistically significant treatment differences in basal, prandial, or total insulin doses at baseline and Week 52 (**Table 16**). At Week 52, the mean HbA1c did not differ between treatment arms (LY900014 = 7.54%; Humalog = 7.47%).

Reviewer comment: *While the HbA1c was higher at week 52 than 26, this is unlikely due to loss of treatment effect. An equal rise in HbA1c occurred in both treatment arms, likely from less strict adherence to diet and/or compliance with medication during the long-term maintenance phase when study visits and contact with study/medical personnel occurred at less frequent time intervals.*

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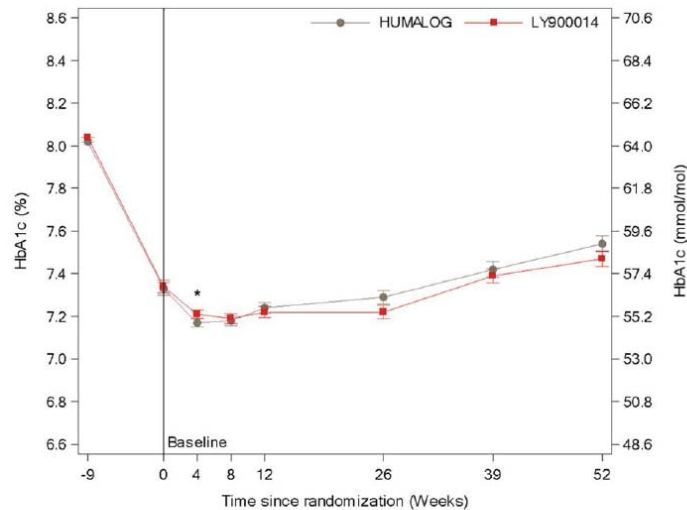
Table 16: Summary and Analysis of Insulin Dose (U/day and U/kg/day) Prior to Discontinuation of IP Week 52 Study ITRM

Timepoint		Treatment Group	n	LSM (SE)	LSM Diff (95% CI), p-value
Basal					
Baseline	U/day	Humalog	423	28.5 (0.76)	1.0 (-1.0, 3.1), p=0.329
		LY900014	435	29.5 (0.74)	
	U/kg/day	Humalog	423	0.36 (0.008)	0.01 (-0.01, 0.03), p=0.274
		LY900014	435	0.37 (0.008)	
Week 52	U/day	Humalog	322	29.7 (0.45)	0.2 (-1.0, 1.4), p=0.726
		LY900014	353	29.9 (0.43)	
	U/kg/day	Humalog	322	0.37 (0.006)	0.00 (-0.01, 0.02), p=0.665
		LY900014	353	0.38 (0.006)	
Bolus					
Baseline	U/day	Humalog	433	31.4 (0.86)	-1.0 (-3.4, 1.4), p=0.405
		LY900014	443	30.3 (0.85)	
	U/kg/day	Humalog	433	0.40 (0.010)	-0.01 (-0.04, 0.02), p=0.534
		LY900014	443	0.39 (0.010)	
Week 52	U/day	Humalog	331	32.3 (0.68)	0.1 (-1.6, 1.8), p=0.916
		LY900014	352	32.4 (0.67)	
	U/kg/day	Humalog	331	0.41 (0.008)	0.01 (-0.01, 0.03), p=0.385
		LY900014	352	0.42 (0.008)	
Total					
Baseline	U/day	Humalog	420	60.0 (1.38)	-0.1 (-3.9, 3.6), p=0.939
		LY900014	434	59.8 (1.35)	
	U/kg/day	Humalog	420	0.76 (0.014)	0.00 (-0.04, 0.04), p=0.963
		LY900014	434	0.76 (0.014)	
Week 52	U/day	Humalog	317	62.1 (0.85)	0.4 (-1.8, 2.6), p=0.701
		LY900014	346	62.5 (0.84)	
	U/kg/day	Humalog	317	0.78 (0.010)	0.01 (-0.01, 0.04), p=0.312
		LY900014	346	0.80 (0.010)	

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

Source: CSR ITRM 52-week Table ITRM.11.3

Figure 7: HbA1c from lead-in to Week 52 prior to discontinuation of IP



Abbreviations: HbA1c = hemoglobin A1c; IP = investigational product; LSM = least squares mean; MMRM = mixed-effects model for repeated measures; SE = standard error.
Data are mean at study entry and LSM (SE) at other visits
* $p < 0.05$ for pairwise comparison of LY900014 versus Humalog

Source: CSR ITRM Figure: ITRM.11.1.

Additional Analyses Conducted on the Individual Trial

Continuous Glucose Monitoring (CGM)

The applicant conducted a sub-study in ITRM, where subjects utilized a continuous glucose monitoring (CGM) device (Dexcom G4 Platinum Sensor, Transmitter, Receiver) used in the blinded mode with glucose alerts deactivated. The primary objective of this study was to compare double-blind LY900014 and Humalog with respect to the $iAUC_{0-2hrs}$ after breakfast obtained from up to 14 days of CGM use at Week 26. Secondary objective included comparison of LY+20, LY900014 and Humalog with respect to the $iAUC_{0-2hrs}$ after breakfast obtained from up to 14 days of CGM use at Week 26; additional objectives included comparison between treatment arms of duration of time glucose values are with various target ranges.

Reviewer comment:

(b) (4)

Because the sub-study includes only a subset of the study participants of ITRM, and only a subset of the CGM participants with sufficient data collected during CGM use could be used for these analyses⁴, the findings obtained from this sub-study might not be generalizable. Additionally, the methods of evaluating TIR and the clinical significance of TIR endpoints are not

⁴ Per CGM sub-study protocol for ITRM, a valid CGM day had to meet both of the following conditions:

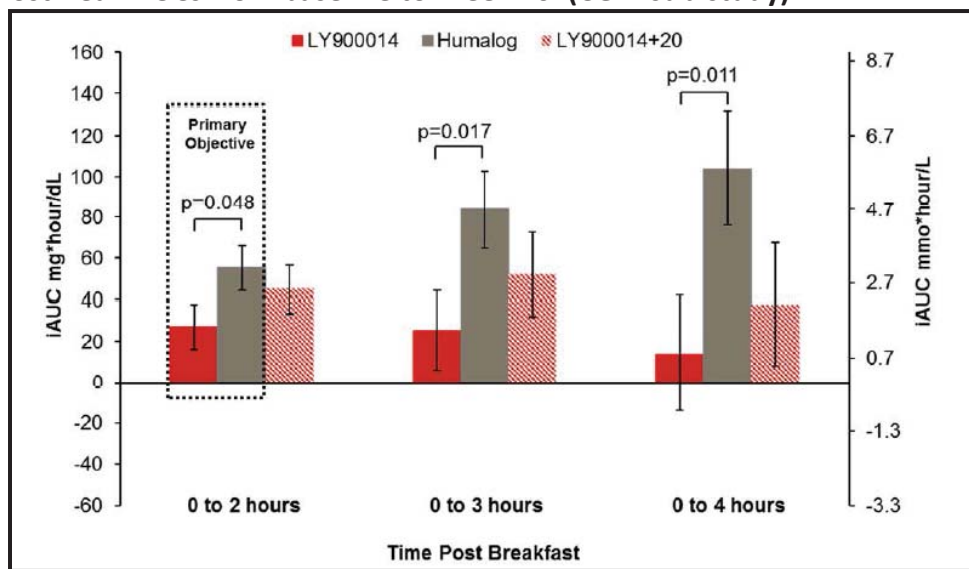
- Minimum number of measures per day – at least 70% of the 288 measures obtained.
- Maximum allowable missing interval – no interval greater than 3 hours between nonmissing measures.

yet established for regulatory decision making.

(b) (4)

Figure 8 illustrates the results of the incremental glucose AUC after breakfast at Week 26. LY900014 significantly reduced the $iAUC_{0-2hrs}$ after breakfast at Week 26 when compared to Humalog (LY900014, 27.1 mg^*h/dL ; Humalog, 55.3 mg^*h/dL ; relative reduction $\sim 51\%$) and significant reductions continued for comparisons of $iAUC_{0-3hrs}$ (LY900014, 25.2 mg^*h/dL ; Humalog, 83.9 mg^*h/dL ; relative reduction $\sim 70\%$) and $iAUC_{0-4hrs}$ (LY900014, 14.0 mg^*h/dL ; Humalog, 104.1 mg^*h/dL ; relative reduction $\sim 87\%$).

Figure 8: Postmeal iAUCs from baseline to Week 26. (CGM sub-study)



Abbreviations: iAUC = incremental area under the curve; LSM =least squares mean; SE = standard error.
Data are LSM (SE)

Source: CSR ITRM Addendum CGM Figure ITRM.9.2.

Reviewer comment: The directionality and the outcomes of the AUC analyses for all treatment arms were congruent with directionality of PPG noted following the MMTT at Week 26 in **Figure 5**. These data are supportive of the efficacy of LY900014 to Humalog in change in PPG excursion at 1 and 2 hours; however, the link between a modifying effect on PPG excursions on clinical outcomes is not sufficiently strong to consider the use of this PD endpoint as a surrogate for efficacy.

6.2. Study ITRN

Study title: A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro, Both in Combination with Insulin Glargine or Insulin Degludec in Adults with Type 2 Diabetes PRONTO-T2D

6.2.1. Study Design

Overview and Objective

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.

Multiplicity-adjusted objectives included demonstrating that LY900014 was:

- superior to Humalog in controlling 1-hour and 2-hour postprandial glucose excursions following MMTT when administered as prandial insulin;
- superior to Humalog on glycemic control as measured by change from baseline to Week 26 in HbA1c when administered as prandial insulin.

Trial Design (see Figure 9)

ITRN was a 26-week, Phase 3, prospective, randomized, multinational, parallel, active-controlled study which compared treatment with LY900014 or Humalog in patients with T2D in combination with basal insulin glargine or degludec. The study had 2 double-blind groups to allow comparison of LY900014 and Humalog when injected at the start of the meal

Study Periods:

Study ITRN included a 1-week **screening period**, an 8-week **lead-in period**, followed by a 26-week **treatment period**, and a 4-week **safety follow-up period**. All patients who completed the 4-week safety follow-up visit (Visit 801; Week 30) and had treatment-emergent insulin lispro antibodies that had not returned to the prespecified baseline range (Visit 2; Week -8) were asked to participate in follow-up to monitor insulin lispro antibody levels for up to 26 weeks after Visit 801.

During the **lead-in period** (Week -8 to 0), all patients received nutrition counseling were provided with a study glucose meter and monitoring supplies in order to perform SMBG. Patients were permitted to continue use of metformin and/or SGLT2 inhibitor therapy. The doses of metformin and/or SGLT2 inhibitor therapy remained stable during the study, unless reduced or discontinued for reasons of safety. Other pre-study oral anti-hyperglycemic medications (OAMs) were discontinued at the beginning of lead-in period. All patients were switched to Humalog insulin for prandial insulin. Patients taking premixed insulin or basal insulin other than insulin glargine or degludec were switched to insulin glargine U-100 once or twice daily, or insulin degludec U-100 or U-200 once daily for basal insulin, as determined by the investigator. Patients remained on the same basal insulin regimen throughout the trial. The purpose of the lead-in period was to titrate basal, obtain preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates.

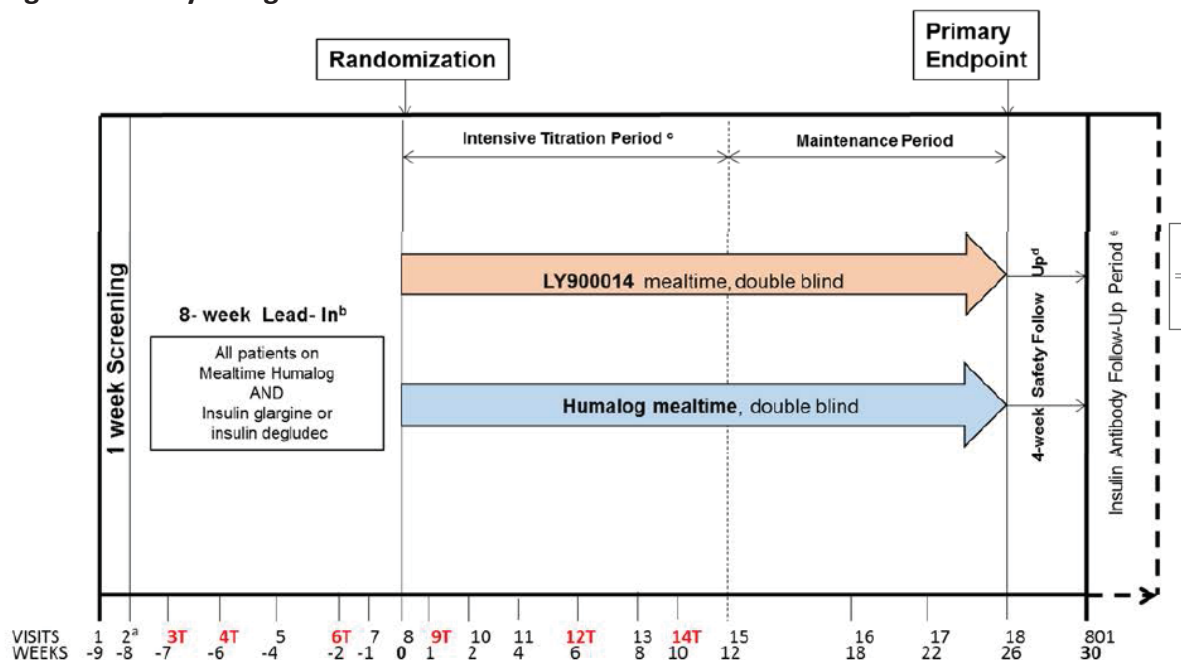
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At **randomization** (Week 0), subjects were randomized in a 1:1 ratio to either LY900014 at mealtime or Humalog at mealtime. Randomization stratification factors included the following: country; HbA1c ($\leq 8.0\%$ or $> 8.0\%$) at end of lead-in period; basal insulin (glargine U-100 or degludec [U-100 or U-200]) during lead-in; number of prandial insulin doses at study entry (<3 , ≥ 3).

During the **intensive titration period** (Week 0 to 12), prandial insulin doses were adjusted as necessary to meet the target SMBG levels based on titration algorithms provided in the protocol. Basal insulin was titrated as needed to facilitate optimal prandial dosing or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

During the **maintenance period** (Week 12 to 26), the prandial insulin and basal doses were adjusted only to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

Figure 9: Study Design Protocol ITRN



Abbreviations: T = telephone visit; U-100 = 100 U/mL; U-200 = 200 U/mL; wk = week.

^a At Visit 2, patients treated with insulin aspart, insulin glulisine, regular insulin, or premixed insulin were transferred to Humalog. At Visit 2, patients treated with a basal insulin regimen other than insulin glargine U-100 or insulin degludec were transferred to an allowed study basal regimen of insulin glargine U-100 once or twice daily or insulin degludec U-100 or U-200 once daily. At Visit 8, patients were randomized to either Humalog or LY900014 and continued their basal insulin regimen.

^b Titrate basal insulin.

^c Titrate prandial insulin (Humalog or LY900014).

^d Patients discontinued study insulins at Week 26.

^e Eligible patients had visits at approximately 3-month intervals for up to 26 weeks after Visit 801 for follow-up of insulin lispro antibody levels.

Source: ITRN CSR Figure ITRN.9.1

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Procedures and study schedule:

See **Table 43** for Schedule of Assessments and details discussed under **Section 6.1.1**.

Trial locations:

The trial was conducted in 131 centers in the following 15 countries: U.S., Argentina, Australia, Czech Republic, Germany, Hungary, India, Italy, Japan, South Korea, Mexico, Russia, Slovakia, Spain, Taiwan.

Key inclusion criteria:

- adults ≥ 18 years of age with T2D for at least 1 year prior to screening
- using insulin continuously for at least 90 days at screening
- on MDI therapy with basal insulin (insulin glargine U-100 or U-300; insulin detemir; insulin degludec U-100 or U-200; NPH insulin) in combination with at least 1 prandial injection of bolus insulin (insulin lispro U-100 or U-200; insulin aspart; insulin glulisine; regular insulin) OR premixed insulin regimen (any basal and bolus insulin combination) injected at least twice daily
- may have been treated with up to 3 oral anti-hyperglycemic medications, on stable doses, for at least 90 days prior to screening (metformin, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium glucose cotransporter 2 (SGLT2) inhibitor, sulfonylurea, meglitinide, alpha-glucosidase inhibitor)
- body mass index (BMI) of ≤ 45.0 kg/m² at screening
- females of childbearing potential not pregnant, not breastfeeding, and on reliable contraception
- HbA1c $\geq 7.0\%$ and $\leq 10.0\%$

Key exclusion criteria:

- diagnosis of T1D or Latent Autoimmune Diabetes in Adults
- diagnosis of secondary diabetes (e.g., hemochromatosis, acromegaly, chronic pancreatitis, or pancreatectomy)
- hypoglycemia unawareness
- >1 episode of severe hypoglycemia within 6 months of screening
- >1 emergency room visit or hospitalization due to diabetic ketoacidosis or hyperglycemic hyperosmolar state within 6 months of screening
- excessive insulin resistance (total daily dose of insulin >2.0 U/kg at screening)
- history of bariatric surgery including Roux-en-Y gastric bypass surgery, gastric banding, and/or gastric sleeve
- renal transplant, dialysis, or serum creatinine > 2.0 mg/dL at screening
- significant cardiac or gastrointestinal disease or liver disease
- history of cancer within previous 5 years (exception of basal cell or squamous cell carcinoma)
- history of blood transfusion or severe blood loss within 90 days prior to screening

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- hemoglobinopathy, anemia, or other traits known to interfere with measurement of HbA1c
- excessive insulin resistance at screening (total daily insulin dose >1.5 U/kg)
- use of thiazolidinediones, GLP-1 receptor agonist, pramlintide, human insulin inhalation powder (Afrezza), or CSII within 90 days prior to screening
- treatment with weight loss drugs (e.g., liraglutide, lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion; or over-the-counter weight loss medications) within 90 days prior to screening
- chronic (> 14 consecutive days) systemic glucocorticoid therapy at pharmacological doses within 8 weeks preceding screening (exception of replacement therapy for adrenal insufficiency)

Reviewer comment: *In general, the inclusion and exclusion criteria appear appropriate. The lower HbA1c threshold of 7.0% for inclusion in study participation may make the assessment of treatment effect more challenging in patients with values in this lower range. Risk to patients was appropriately minimized by the exclusion of participants with hypoglycemia unawareness and/or a 6-month history of clinically significant hyperglycemia and/or DKA. The study permitted continued use of metformin and SGLT2 inhibitors for patients who were previously receiving these widely prescribed OAMs. Since metformin is first-line therapy in patients with T2D and potential cardiovascular benefits are provided with SGLT2 inhibitor therapy, continuation of these agents during study participation is appropriate. The study excluded patients on thiazolidinedione who are at risk for edema with concomitant insulin therapy. Concomitant use of sulfonylurea and meglitinide, which can increase risk of hypoglycemia, was not permitted. While DDP-4 inhibitor and alpha-glucoside inhibitors do not independently cause hypoglycemia, they have small treatment effects and exclusion of these agents during study participation to minimize confounding factors in interpretation of hypoglycemia and efficacy seems reasonable. Additionally, patients requiring MDI insulin therapy are less likely to benefit from these agents. The study also excluded patients on GLP-1 receptor agonist therapy and pramlintide. It's not specified why these therapies were not permitted. It's possible administration of additional injectable agent may lead to less compliance with MDI insulin therapy or possibly medication errors during the trial. Since both agents may potentially reduce insulin requirements and may affect appetite, exclusion of these agents may also minimize confounding factors in efficacy analysis. Similarly, use of other weight loss therapies were also an exclusion criterion.*

Insulin dosing, monitoring and titration:

Investigators used SMBG levels to make treatment decisions to achieve glycemic goals (see **Table 6**). The prescribed insulin doses during the study were individualized and were determined by and were the responsibility of the investigator.

Basal insulin:

During the lead-in period (Week -8 to 0), the patients' basal insulin was titrated every 3 to 4

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days as necessary using the titration algorithm to reach the FBG target of 100 mg/dL (see **Table 17**). Basal insulin dose was adjusted if needed to facilitate optimal prandial insulin dosing during the insulin intensive titration period (Weeks 0 to 12) or for safety reasons. Thereafter, during the maintenance period (Weeks 12 to 26), adjustments to basal insulin doses were made to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

Table 17: Basal Insulin Adjustments Algorithm for ITRN

If median (middle) FBG from the 3 previous FBG values is:	Adjust the basal dose by:
≤80 mg/dL	Decreasing dose to previous lower dose ^a
80-109 mg/dL	No adjustment
130-149 mg/dL	Increasing by 2-4 units
150-179 mg/dL	Increasing by 4-6 units
≥180 mg/dL	Increasing by 6-8 units

Abbreviation: FBG = fasting blood glucose.

^a If there is no previous dose because this was the first assigned dose, then the basal dose should be decreased by 10% in consultation with the investigator.

Source: Protocol ITRN Table ITRN.5.

Prandial insulin:

Prandial insulin for Study ITRN was managed and titrated similar to Study ITRN (see details discussed in **Section 6.1.1**).

Subject completion, discontinuation, withdrawal criteria:

See discussion of this information in **Section 6.1.1**.

Treatment compliance:

No specific study data were collected for the analysis of treatment compliance in this study.

Study Endpoints

Primary endpoints:

Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c

Multiplicity adjusted endpoints:

- Difference between LY900014 and insulin lispro in the 1-hour PPG excursion (serum glucose measured 1 hour after the start of the meal minus fasting serum glucose) from a MMTT at Week 26
- Difference between LY900014 and insulin lispro in the 2-hour PPG excursion (serum glucose

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measured 2 hours after the start of the meal minus fasting serum glucose) from an MMTT at Week 26

- Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c

Safety endpoints:

See discussion of this information in **Section 6.1.1**.

Statistical Analysis Plan

See discussion of this information in **Section 6.1.1**.

Protocol Amendments

The protocol was amended 5 times prior to enrollment of patients with minor revisions to satisfy foreign regulatory agency requirements.

6.2.2. Study Results

Compliance with Good Clinical Practices

All studies were conducted in compliance with the International Conference on 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 a Form FDA 3454 for all covered clinical studies. See discussion financial disclosure information in **Section 6.1.2** and **Section 13.2**.

Patient Disposition

In Study ITRN, 963 patients were screened, and 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).

Of the patients who discontinued the studies early during the treatment period, the most common reason for treatment discontinuation was withdrawal by subject. There were no statistically significant treatment differences in the treatment arms of the number of patients discontinuing treatment or in the reasons for treatment discontinuation. Patient disposition and reasons for discontinuation are summarized in **Table 9**.

Demographic and Baseline Disease Characteristics (see Table 18)

The demographics of the study population revealed the mean age of patients of approximately 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/m². 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%).

Table 18: Summary of Demographic and Diabetes Characteristics Study ITRN

Parameter	Humalog (N=337)	LY900014 (N=336)	Total (N=673)	p-value ^a
Sex, n (%)				
Female	162 (48.1)	152 (45.2)	314 (46.7)	0.461
Male	175 (51.9)	184 (54.8)	359 (53.3)	
Age (years)				
Mean (SD)	60.99 (9.24)	60.17 (9.38)	60.58 (9.31)	0.254
Minimum, maximum	28, 84	34, 83	28, 84	
Age group, n (%)				
<65 years	194 (57.6)	212 (63.1)	406 (60.3)	0.143
≥65 years	143 (42.4)	124 (36.9)	267 (39.7)	
<75 years	327 (97.0)	327 (97.3)	654 (97.2)	0.821
≥75 years	10 (3.0)	9 (2.7)	19 (2.8)	
Race, n (%)				
Asian	81 (24.0)	83 (24.7)	164 (24.4)	0.773
Black or African American	16 (4.7)	14 (4.2)	30 (4.5)	
White	229 (68.0)	233 (69.3)	462 (68.6)	
Ethnicity, n (%)				
Hispanic or Latino	78 (23.1)	79 (23.5)	157 (23.3)	0.680
Not Hispanic or Latino	208 (61.7)	214 (63.7)	422 (62.7)	
BMI (kg/m ²)				
Mean (SD)	32.44 (5.79)	32.12 (5.66)	32.28 (5.73)	0.474
Minimum, maximum	18.78, 45.37	19.90, 47.60	18.78, 47.60	
Duration of diabetes (years)				
Mean (SD)	16.56 (7.88)	16.44 (7.76)	16.50 (7.82)	0.836
Minimum, maximum	1.47, 40.16	1.50, 44.15	1.47, 44.15	
HbA1c, mean (SD)				
Study entry (%)	8.30 (0.75)	8.30 (0.79)	8.30 (0.77)	1.000

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Baseline (%)	7.31 (0.72)	7.27 (0.68)	7.29 (0.70)	0.459
FSG, mean (SD)				
Study entry (mg/dL)	163.77 (55.84)	160.57 (56.32)	162.16 (56.06)	0.463
Baseline (mg/dL)	123.43 (36.86)	123.31 (33.38)	123.37 (35.14)	0.964
Prestudy basal insulin, n (%)				0.749
Insulin glargine	182 (63.2)	197 (68.2)	379 (65.7)	
NPH	33 (11.5)	32 (11.1)	65 (11.3)	
Insulin degludec	35 (12.2)	29 (10.0)	64 (11.1)	
Insulin detemir	38 (13.2)	31 (10.7)	69 (12.0)	
Baseline basal insulin, n (%)				0.833
Insulin glargine	257 (76.3)	260 (77.4)	517 (76.8)	
Insulin degludec	80 (23.7)	76 (22.6)	156 (23.2)	
Baseline OAMs, n (%)				0.246
Metformin	231 (68.5)	244 (72.6)	475 (70.6)	
SGLT-2 inhibitor	54 (16.0)	65 (19.3)	119 (17.7)	
Number bolus injections prestudy				0.876
<3/day, n (%)	85 (25.2)	83 (24.7)	168 (25.0)	
≥3/day, n (%)	252 (74.8)	253 (75.3)	505 (75.0)	
Region, n (%)				0.876
United States	91 (27.0)	90 (26.0)	181 (26.9)	
Asia	78 (23.1)	78 (23.2)	156 (23.2)	
Europe	100 (29.7)	102 (30.4)	202 (30.0)	
South America	61 (18.1)	58 (17.3)	119 (17.7)	
Other	7 (2.1)	8 (2.4)	15 (2.2)	

Abbreviations: BMI = body mass index; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; N = number of patients in population; n = number of patients in the category; NPH = neutral protamine Hagedorn; OAM = neutral protamine Hagedorn; SD = standard deviation; SGLT-2 = sodium glucose cotransporter 2.

a p-value for overall treatment effect.

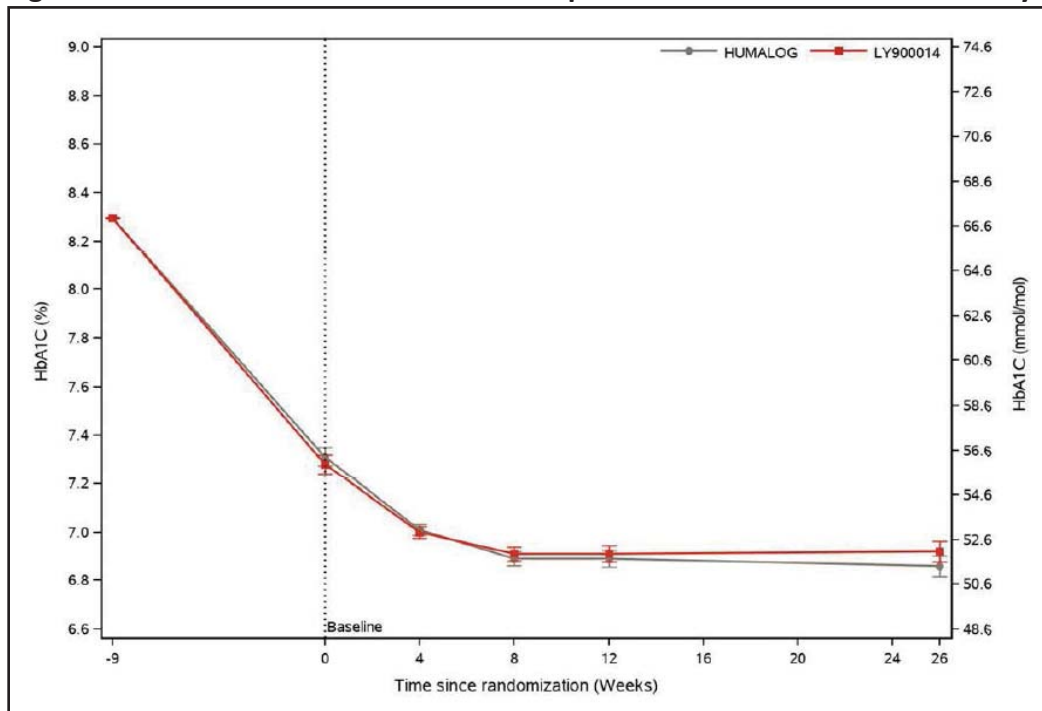
Source: Table ITRN.11.1 CSR ITRN

Reviewer comment: Treatment arms were balanced in terms of race, ethnicity, BMI, and duration of diabetes. African Americans are underrepresented, in comparison to the US population; however, I do not think this racial imbalance had any significant effect on the outcome of the study or the generalizability of the study results to the US population. The baseline characteristics and demographics otherwise appear representative of the US population and T2D population. The LY900014 treatment arm had slightly more men than women in comparison to the Humalog arm. While the mean age is similar between treatment arms, it is noted that the LY900014 treatment arm had a slightly greater percentage of patients under age 65 years in comparison to the Humalog arm (LY900014, 63.1%; Humalog 57.6%). Similarly, a numerically higher percentage of patients were on OAMs in the LY900014 treatment arm compared to Humalog arm (metformin: LY900014, 72.6%; Humalog 68.5%) (SGLT-2 inhibitor: LY900014, 19.3%; Humalog, 16.0%). Given that OAMs enhance the treatment effect in terms of HbA1c reduction, this difference may favor the LY900014 treatment arm. I do not believe, however, that this small imbalance had any significant effect on the efficacy outcome of this study, as the study design allowed for the doses of LY900014 and Humalog to be titrated as necessary to achieve glycemic goals.

Overview of Change in HbA1c During Study Periods

Figure 10 illustrates that similar changes in HbA1c occurred during the lead-in period (week -8 to 0) in both treatment arms. More modest and similar reductions occurred the intensive titration period (week 0 to 12), and HbA1c generally remained stable during the maintenance period (week 12 to 26) for both treatment arms.

Figure 10: HbA1c from lead-in to Week 26 prior to discontinuation of IP Study ITRN



Source: CSR ITRN Figure ITRN.11.1

Table 11 provides a summary of the change in HbA1c from baseline to Week 26 for LY900014 and Humalog.

Reviewer comment: Similar to the results in Study ITRM, most of the reduction in HbA1c occurred during the lead-in phase (as illustrated in **Figure 10** and **Table 11**) when nutritional counseling, guided insulin titration, and regular visits with medical/study personnel were initiated. HbA1c remained stable after insulin titration was completed, suggesting that patient compliance continued throughout the 26-week study.

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Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. In Study ITRN, dosing with LY900014 20 minutes after meal was not studied. See **Section 7.3** for discussion of extrapolation of effectiveness of postmeal dosing to the T2D population.

Table 19 presents a summary of the FDA⁵ efficacy analysis for change in HbA1c from baseline for LY900014 and Humalog. **Table 20** summarizes the FDA efficacy results of change in PPG excursion following MMTT between treatment arms. **Table 21** provides a summary of the Applicant’s primary and multiplicity adjusted efficacy results of change in PPG excursion following MMTT between treatment arms.

Table 19: Primary Analysis Outcome 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 submitted by Applicant and corroborated by FDA Statistical Reviewer

⁵ The analyses were conducted using all randomized subjects, submitted by the Applicant, and corroborated by FDA Statistical reviewer.

Table 20: MMTT PPG measurements at hour 1 and 2 Study ITRN

Treatment	Humalog N = 337	LY900014 N = 336	PPG hour
Baseline PPG excursion* Mean (std)	70.4(43.69)	58.5 (48.48)	1
Change in PPG (95% CI)	-6.55 (-10.99, -2.11)	-18.44 (-22.89, -13.99)	1
LY900014-Humalog (95% CI)	-11.89 (-18.18, -5.59)		1
Baseline PPG excursion* Mean (std)	94.7(92.8)	77(70.2)	2
Change in PPG (95% CI)	-4.78 (-10.32, 0.76)	-22.34 (-27.87, -16.81)	2
LY900014-Humalog (95% CI)	-17.55 (-25.39, -9.72)		2

*Results based on MMTT at the beginning of the trial
Source: Excerpted from Statistical Review BLA 761109

Table 21: Summary of Primary and Multiplicity Adjusted Efficacy Results for Study ITRN Using the Graphical Approach (ITT Estimand)

Hypothesis	Test	LSM (SE)		LY-Humalog LSM Difference (95% CI)	p-Value	NIM	Objective Met?
		Humalog	LY900014				
Primary Objective							
(H1) Change in HbA1c (%)	NI	-0.46 (0.05)	-0.43 (0.05)	0.03 (-0.08,0.13)		0.4%. 0.3%	Yes
Multiplicity-Adjusted Secondary Objectives							
(H2) Change 1 hr PPG excursion (mg dL)	SP	74.6 (3.56)	62.6 (3.56)	-12.0 (-18.3, -5.7)	<0.001		Yes
(H3) Change 2 hr PPG excursion (ma dL)	SP	97.9 (4.43)	80.3 (4.43)	-17.6 (-25.4,-9.8)	<0.001		Yes
(H4) Change in HbA1c (%)	SP	-0.46 (0.05)	-0.43 (0.05)	0.03 (-0.08,0.13)	0.624		No

Abbreviations: CI = confidence interval; PPG = postprandial glucose; H = hypothesis; HbA1c = hemoglobin A1c; ITT = intent-to-treat; LSM = least-squares mean; NI = noninferiority comparison; NIM = noninferiority margin; SE = standard error; SP = superiority comparison;

Source: CSR ITRN modified from Table ITRM.11.2

(H1) 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%.

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(H4) 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.

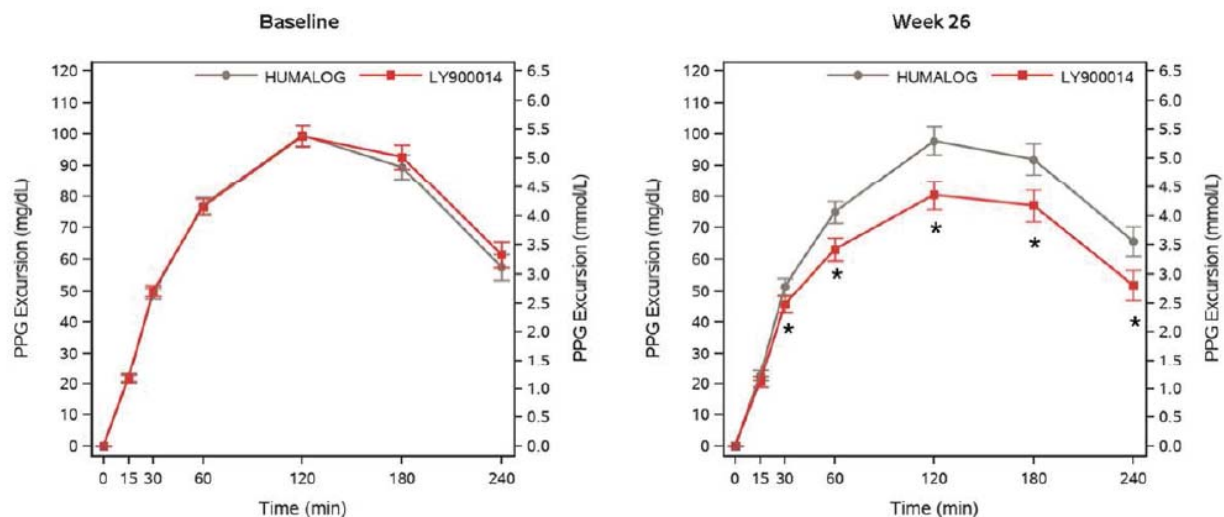
Reviewer comment: The primary objective of the study of demonstrating noninferiority of LY900014 to Humalog in in glycemic control was achieved; however, superiority of LY900014 to Humalog (H4) was not demonstrated.

Efficacy Results – Secondary and other relevant endpoints

(H2) and (H3) 1-hour and 2-hour PPG excursions LY900014 vs Humalog: In both the Applicant's and FDA analyses, LY900014 was superior to Humalog in controlling 1-hour and 2-hour PPG excursions during MMTT:

- 1-hour: LSM Difference (95% CI) = -11.89 mg/dl (-18.18, -5.59)
- 2-hour: LSM Difference (95% CI) = -17.55 mg/dl, (-25.39, -9.72)

Figure 11: Time course of blood glucose excursion during mixed-meal tolerance test from randomization to Week 26 prior to discontinuation of IP Study ITRN



Note: Data are LSM (SE).

Abbreviations: IP = investigational product; LSM = least squares mean; PPG = postprandial glucose; SE = standard error.

*p<0.05 at 30 minutes; p<0.001 at 60, 120, and 180 minutes; and p=0.001 at 240 minutes.

Source: CSR ITRN Figure ITRN.11.2

Reviewer comment: As demonstrated in **Figure 11**, PPG excursions following MMTT were statistically significantly lower with LY900014 treatment compared to Humalog treatment from all timepoints beginning at 30 minutes and continuing to 240 minutes. As seen with Study ITRM, although HbA1c reductions are similar, mealtime LY900014 demonstrates superior control of PPG excursions than Humalog.

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Proportions of Patients Achieving HbA1c Targets:

Overall, there were no significant treatment differences between the LY900014 and Humalog groups in the percentages of patients achieving HbA1c targets ($\leq 6.5\%$ and $< 7\%$) at Week 26.

- $< 6.5\%$: Humalog, n= 120 (35.8%); LY900014, n=123 (36.8%)
- $< 7\%$: Humalog, n= 178 (53.1%); LY900014, n=190 (56.9%)

Changes in Insulin Doses:

Table 22 presents a summary of basal, bolus, and total insulin dose at baseline and Week 26.

- For basal insulin dose, there were no statistically significant treatment differences at baseline and Week 26.
- For prandial insulin dose, there were no statistically significant treatment difference at baseline. For Week 26, the daily dose (U/day) for LY900014 group was statistically significantly higher than in the Humalog group (LY900014, 53.2 U/d; Humalog 49.5 U/d, $p=0.037$).
- For total insulin dose, there was no statistically significant treatment difference at baseline. For Week 26, the daily dose (U/day) for LY900014 group was statistically significantly higher than in the Humalog group (LY900014, 106.5 U/d; Humalog 101.2 U/d, $p=0.038$).

Figure 12 illustrates the mean daily basal, prandial, and total daily insulin doses from baseline to Week 26, demonstrating that the titration pattern was similar in both treatment arms.

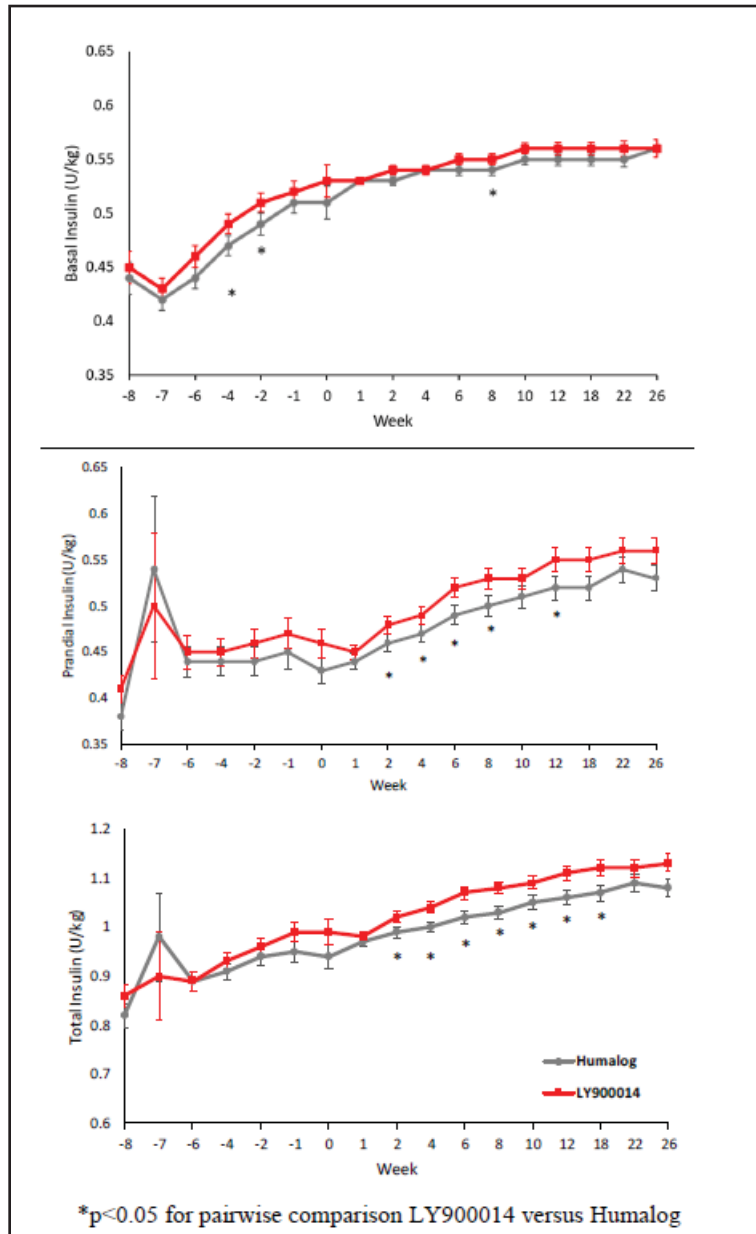
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Table 22: Summary and Analysis of Insulin Dose (U/day and U/kg/day) Study ITRN

Time Point		Treatment Group	n	LSM (SE)	LSM Difference (95% CI)	p-value ^a
Basal						
Baseline	U/day	Humalog	317	46.4 (1.61)	2.9 (-1.5, 7.4)	0.196
		LY900014	323	49.4 (1.60)		
	U/kg/day	Humalog	317	0.51 (0.02)	0.03 (-0.01, 0.07)	
		LY900014	323	0.53 (0.02)		
Week 26	U/day	Humalog	287	52.3 (0.82)	0.4 (-1.8, 2.6)	0.728
		LY900014	297	52.7 (0.81)		
	U/kg/day	Humalog	287	0.56 (0.01)	0.00 (-0.02, 0.02)	
		LY900014	297	0.56 (0.01)		
Bolus						
Baseline	U/day	Humalog	330	39.6 (1.61)	2.6 (-1.9, 7.1)	0.254
		LY900014	330	42.2 (1.61)		
	U/kg/day	Humalog	330	0.43 (0.02)	0.02 (-0.02, 0.07)	
		LY900014	330	0.46 (0.02)		
Week 26	U/day	Humalog	304	49.5 (1.41)	3.7 (0.2, 7.2)	0.037
		LY900014	305	53.2 (1.41)		
	U/kg/day	Humalog	304	0.53 (0.01)	0.03 (0.00, 0.07)	
		LY900014	305	0.56 (0.01)		
Total						
Baseline	U/day	Humalog	316	86.6 (2.87)	4.8 (-3.2, 12.7)	0.238
		LY900014	321	91.4 (2.85)		
	U/kg/day	Humalog	316	0.94 (0.03)	0.04 (-0.02, 0.11)	
		LY900014	321	0.99 (0.03)		
Week 26	U/day	Humalog	284	101.2 (1.93)	5.2 (0.3, 10.2)	0.038
		LY900014	295	106.5 (1.92)		
	U/kg/day	Humalog	284	1.08 (0.02)	0.04 (0.00, 0.09)	
		LY900014	295	1.13 (0.02)		
Abbreviations: ANOVA = analysis of variance; CI = confidence interval; HbA1c = hemoglobin A1c; LSM = least squares mean; MMRM = mixed-effects model for repeated measures; n = number of patients; SE = standard error; U = units.						
^a p-value at baseline is from ANOVA for baseline measures: Variable = treatment (type III sum of squares);						

Source: CSR Study ITRN Table ITRN.11.6.

Figure 12: Mean Basal, Prandial, and Total Daily Insulin Doses (U/kg) over Time Study ITRN



Source: Response to IR September 29, 2019

Reviewer comment: Review of the insulin dose data do not suggest any significant differences in titration patterns. It is notable that while basal insulin doses appeared to be fairly stable after the lead-in period, the prandial insulin doses did not appear to reach equipoise and continued to increase beyond the titration period into the maintenance period. Thus, it doesn't appear that prandial insulin therapy was optimized during the maintenance period, and the HbA1c results

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may not be indicative of the full treatment effect. However, this appeared to be the case for both treatment arms. While numerically, the dose of prandial and total insulin was higher for the LY900014 treatment arm at Week 26 resulting in a statistically significant difference, the difference in total daily insulin was 5.2 units and the total mean U/kg/day was not significantly different between LY900014 and Humalog. In my opinion, this numerical difference is not clinically significant and does not suggest a difference in potency between LY900014 and Humalog.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary efficacy endpoint was change in HbA1c from baseline to Week 26. Study ITRM enrolled patients with T1D, Study ITRN enrolled patients with T2D. Both trials compared mealtime dosing with LY900014 with Humalog. Study ITRM also assessed the treatment effect of dosing LY900014 20 minutes after meals. The results of Dr. Kettermann's analyses for the primary endpoint are presented **Table 12** for Study ITRM and **Table 19** for Study ITRN.

The analyses show that noninferiority of mealtime LY900014 to Humalog was achieved in both trials as the upper limits of the 95% CIs for differences (LY900014-Humalog) were less than the pre-specified noninferiority margin of 0.4%. Noninferiority was also demonstrated with the more stringent noninferiority margin of 0.3% in both trials. The difference in treatment effect of postmeal administration of LY900014 with mealtime Humalog in patients with T1D also met the NIM criterion, although the results demonstrate that the overall difference was statistically significantly inferior for LY900014 as the 95% CI was above zero for this comparison.

While treatment with mealtime LY900014 was found to be statistically superior to Humalog on glycemic control in the T1D study population, the point estimate of the treatment difference (0.08) is minimal with an upper bound of the 95% confidence interval equal to zero and does not translate to a clinically significant difference. Superiority of treatment with mealtime LY900014 to Humalog was not demonstrated in the T2D study.

Reviewer comment: *Despite the statistical superiority of mealtime LY900014 to Humalog in the T1D study, the trivial difference in HbA1c between treatments does not constitute a clinically relevant difference. In addition, superiority was not substantiated in the T2D study.*

(b) (4)

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The efficacy results for mealtime dosing with LY90014 for both the T1D and T2D population achieved statistical noninferiority to Humalog. Treatment with LY+20 was also found to be statistically noninferior (clinically not unacceptably worse) to Humalog for the prespecified NIM of 0.4% as well as 0.3%; therefore, the data from these pivotal trials have provided substantial evidence of effectiveness.

7.1.2. Secondary and Other Endpoints

For both studies, the mean changes in PPG excursion at 1 hour and 2 hours after MMTT at Week 26 were analyzed as secondary endpoints. The analyses were conducted using a mixed-effect model with repeated measures (MMRM). The results of Dr. Kettermann's analyses are presented in **Table 13** for Study ITRM and **Table 20** for Study ITRN.

The results of the analyses show that at week 26, mealtime LY900014 was superior to Humalog for PPG excursion at both, 1 hour and 2 hours after the MMTT (both confidence intervals were below zero) in patients with T1D. Superiority of mealtime LY900014 to Humalog for PPG excursion for both timepoints following MMTT in subjects with T2DM was also achieved.

Reviewer comment: [REDACTED] (b) (4) While these data may be supportive for the efficacy of LY900014, and demonstrate statistical superiority, the significant improvement in PPG was not accompanied by a commensurate difference in treatment effect on HbA1c. The clinical relevance of PPG reduction is not known; [REDACTED] (b) (4)

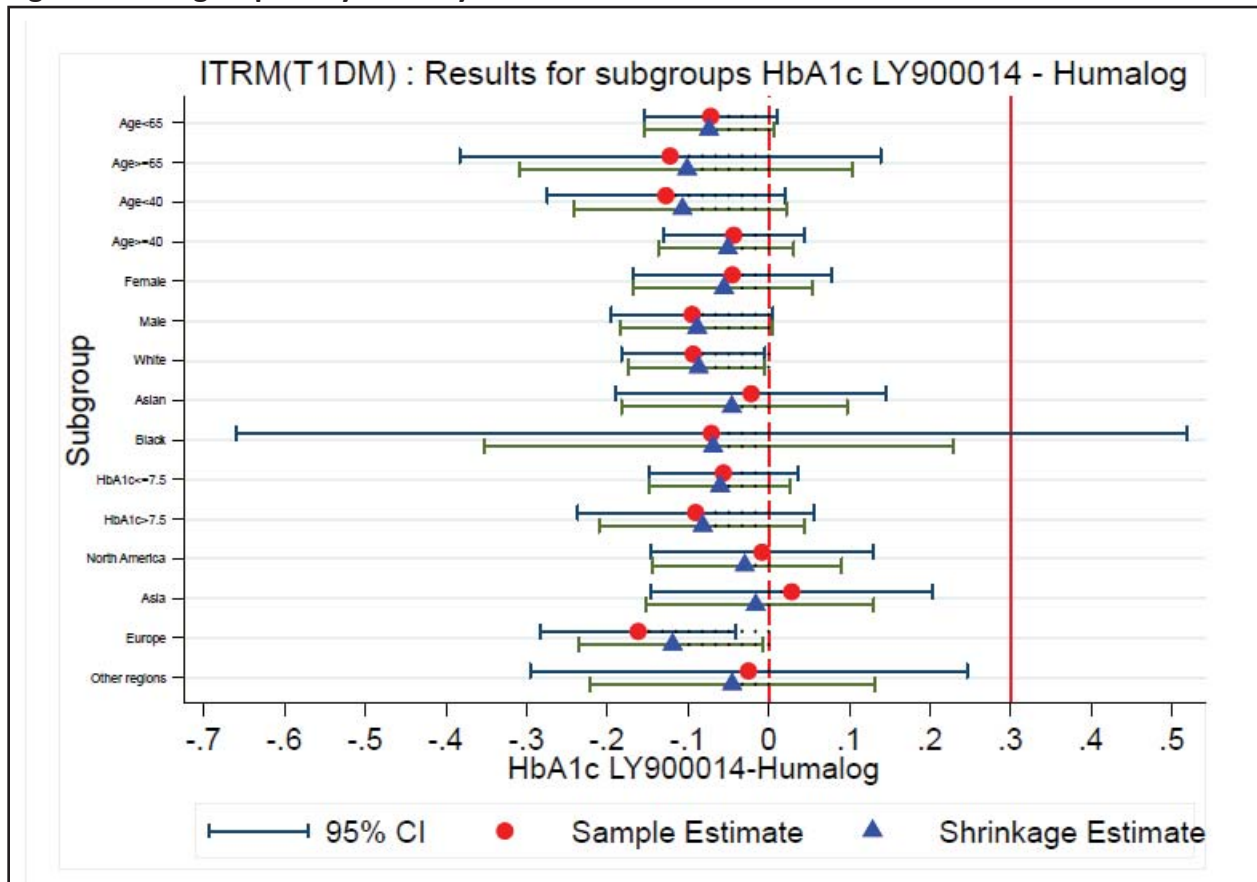
7.1.3. Subpopulations

Dr. Kettermann performed additional subgroup analyses for the primary efficacy endpoint. Sample estimates of treatment effect in change in HbA1c among subgroups were obtained using the ANCOVA model. Additionally, shrinkage estimates of treatment effects were derived using a Bayesian hierarchical model. The results of these analyses did not reveal any evidence of a treatment difference among subgroups in the T1D or T2D population.

In the T1D population, gender (female, male), race (White, Asian, and Black), age (< 65 and ≥ 65 years; < 40 and ≥40 years), baseline HbA1c (≤ 7.5 and >7.5%), and geographic region (North America, Asia, Europe, and Other regions) were analyzed (**Figure 13**).

For subjects with T1D, the subgroup treatment effects were consistent across subgroups and with the overall treatment effect. Only the Black race subgroup had the 95% CI cross the NIM threshold, likely due to the small subgroup size (n=16). Shrinkage analysis provided a new CI that did not cross the NIM.

Figure 13: Subgroup Analysis Study ITRM

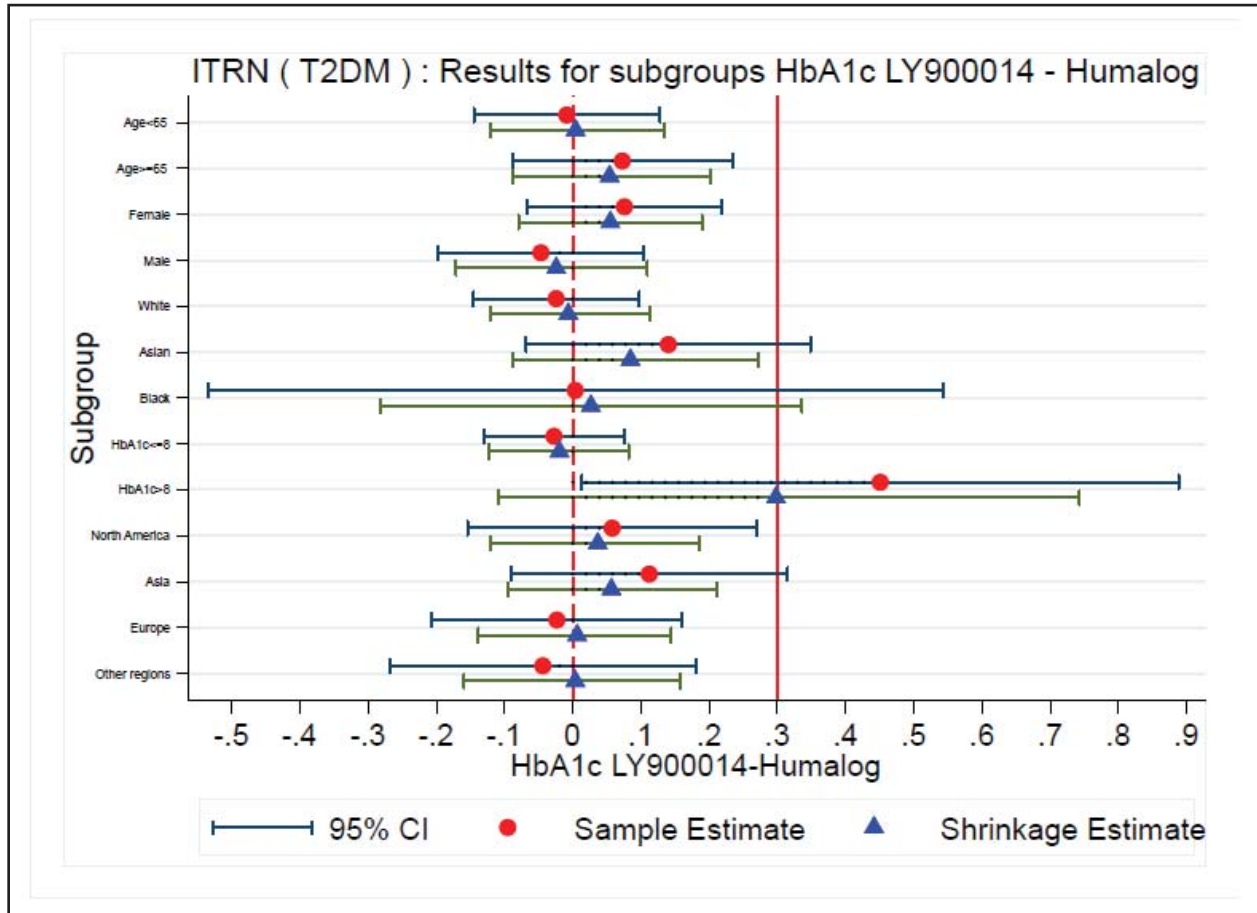


Source: Excerpted from Statistical Review BLA 761109

In the T2D population subgroups included gender (female, male), race (White, Asian, and Black), age (< 65 and ≥ 65 years), baseline HbA1c (≤ 8.0 and >8.0%), and geographic region (North America, Asia, Europe, and Other regions) were analyzed (**Figure 14**).

Among subjects with T2D, the 95% CI for the treatment effect crossed the NIM boundary in the Asian and Black or African American race subgroups and among subjects from Asia; however, the CI for the shrinkage estimate was below the NIM threshold those three subgroups. Since the majority of subjects in ITRN study HbA1c ≤ 8% (n=577), the HbA1c subgroup of >8% did not have a sufficient number of subjects to produce a meaningful effect estimate.

Figure 14: Subgroup Analysis Study ITRN



Source: Excerpted from Statistical Review BLA 761109

7.1.4. Dose and Dose-Response

Both LY900014 and Humalog were titrated to glycemic goals, thus exploration of dose response is not applicable. As discussed in greater detail in **Section 6.1.2** and **Section 6.2.2**, review of insulin titration patterns and changes in basal, prandial, and total insulin doses from baseline to Week 26 in both studies revealed no clinically significant differences between LY900014 and Humalog to suggest a difference in potency between products.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The data from the ITRM 52-week study show that LY900014 was effective up to 12 months. **Figure 7** illustrates that over the course of 52 weeks, in both the Humalog and LY900014

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treatment groups, HbA1c similarly improved during the lead-in and intensive titration phase, remained stable during the maintenance period, and increased marginally during the long-term maintenance period. No statistically significant treatment differences in basal, prandial, or total insulin doses at baseline and Week 52 were noted (**Table 16**). The mean HbA1c did not differ between treatment arms at Week 52 (LY900014 = 7.54%; Humalog = 7.47%). Overall, the onset, duration and durability of efficacy effect of LY900014 appears to be similar to that of Humalog.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Results of Study ITRM demonstrated efficacy of postmeal dosing with LY900014, showing that this treatment is statistically noninferior (clinically not unacceptably worse) than treatment with Humalog on glycemic control based upon change in HbA1c at 26 Weeks. Having another therapeutic option is a benefit to patients with diabetes requiring prandial insulin therapy. An insulin product approved for dosing at the start of a meal or within 20 minutes after starting a meal is also advantageous to patients. Alternative dosing options offer convenience and flexibility for patients when dosing prior to a meal is not possible or is delayed by circumstances. Additionally, dosing after a meal may allow patients to more accurately estimate their carbohydrate intake and calculate their mealtime insulin requirements, which may result in better glycemic control.

7.3. Integrated Assessment of Effectiveness

Study ITRM and Study ITRN provide evidence of efficacy for LY900014 in support of its use for the indication to improve glycemic control in adults with diabetes mellitus. Both studies were able to achieve their primary objectives, demonstrating noninferiority of treatment with mealtime LY900014 to Humalog on glycemic control as measured by change in HbA1c from baseline to Week 26 in patients with T1D and T2D, respectively. In addition, in patients with T1D, noninferiority to treatment with Humalog was also achieved with LY900014 dosed 20 minutes after meals.

Noninferiority to treatment with Humalog was established for mealtime LY900014 in both T1D and T2D populations as well as for postmeal LY900014 dosing in T1D patients. For mealtime LY900014 vs Humalog in T1D, the treatment difference in HbA1c (LY900014-Humalog) was -0.08 with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: -0.16, 0.00). For mealtime LY900014 vs Humalog in T2D, the treatment difference was 0.03 with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: -0.08, 0.13). For postmeal dosing of LY900014 vs Humalog in T1D, the treatment difference was 0.14 with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: 0.05, 0.22). All three analyses were also able to establish noninferiority with the more stringent noninferiority margin of 0.3%.

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Treatment with mealtime LY900014 was found to be statistically superior to Humalog on glycemic control in the T1D study population, as the CI for the difference in treatment effect was less than zero. However, the point estimate of the treatment difference (0.08) is small and does not constitute a clinically significant difference. In addition, superiority was not replicated in the study in patients with T2D.

The Applicant is proposing that patients being treated with LY90004 may be dosed within 20 minutes after starting a meal. Study ITRM demonstrated noninferiority of treatment with LY900014 administered postmeal to mealtime Humalog in glycemic control. Study ITRN did not investigate postmeal dosing of LY900014 in patients with T2D. At the pre-BLA meeting, however, the Applicant proposed that the totality of data from the Phase 3 studies, clinical pharmacology mealtime studies (ITRV and ITRW), including the developmental studies (b) (4) 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. In addition to the data from these studies and the modeling, my 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, I conclude, based on the results from the Phase 3 studies, studies ITRV and ITRW, and the pharmacometric assessment, the data support postmeal dosing in the T2D population as well as the T1D population.

Both Study ITRM and Study ITRN were also able to successfully achieve their secondary objectives, demonstrating superiority of treatment with mealtime LY900014 to Humalog in 1-hour and 2-hour PPG excursion following MMTT after 26 weeks of treatment. For both studies, at both timepoints, both confidence intervals were below zero:

T1D: 1-hour: LSM Difference (95% CI) = -27.63 mg/dl (-34.83, -20.42)
2-hour: LSM Difference (95% CI) = -30.52 mg/dl (-40.50, -20.54)

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T2D: 1-hour: LSM Difference (95% CI) = -11.89 mg/dl (-18.18, -5.59)
2-hour: LSM Difference (95% CI) = -17.55 mg/dl, (-25.39, -9.72)

While the analyses of these data demonstrate statistical superiority and appear to be robust, the link between a modifying effect on PPG excursions on clinical outcomes is not sufficiently strong to consider the use of this PD endpoint as a surrogate for efficacy. Additionally, the relative degree of PPG lowering that is clinically relevant has not been established and therefore, these data are considered exploratory. However, HbA1c is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus.

In summary, the results from these two adequate and well-controlled trials have provided substantial evidence of effectiveness for LY900014 in terms of change in HbA1c, supporting the proposed indication (to improve glycemic control in adults with diabetes mellitus) and the proposed flexible dosing (administer LY900014 by SC injection at the start of a meal or within 20 minutes after starting a meal).

8. Review of Safety

8.1. Safety Review Approach

The safety evaluation for this BLA based on clinical data submitted for the pivotal MDI trials, ITRM and ITRN. Additional exposure and supportive safety data were provided from CSII trial ITSI. Study ITSI was a Phase 3, prospective, randomized, double-blind, 2-treatment group, 2-period (6-week treatment each) crossover design trial that evaluated the safety and compatibility of LY9000014 compared to Humalog in the treatment of patients with T1D when administered via CSII.

During the Phase 3 trials, the safety data collected for LY900014 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 and MAED, I analyzed these datasets for safety signals and performed additional subgroup analyses to explore differences between LY900014 and comparator, as described in the relevant subsections.

Safety data (except hypoglycemia) from Studies ITRM and ITRN were integrated. Given the similarity in the duration, design, and comparator in these studies, pooling of the safety data enhances detection of an association between LY900014 and an AE. However, differences in the dosing regimen (Study ITRM included a postmeal dosing arm and Study ITRN did not) and

population (Study ITRM enrolled T1D and Study ITRN enrolled T2D) warrant looking at differences in certain safety parameters, such as dropouts and deaths, separately. Review of treatment discontinuations and study discontinuations in both ITRM and ITRN revealed no differences between dosing regimens or study populations in the rates or reasons for discontinuation (summarized in **Table 9**). Similarly, no differences between groups were noted in the deaths that occurred: 3 occurred in Study ITRM (1 Humalog, 1 LY900014, 1 LY+20) and 3 in Study ITRN (1 Humalog, 2 LY900014) (discussed in greater detail in **Section 8.4.1**).

The 26-week integrated dataset pools 26-week safety data from Studies ITRM and ITRN, at the time of primary efficacy outcome. The 52-week integrated dataset pools 26-week safety data from Study ITRN with 52-week safety data from Study ITRM. The 52-week integrated dataset also includes the safety follow-up period, while the 26-week dataset does not. In the integrated dataset, “All LY” (n=1116) represents LY900014, administered either 0 to 2 minutes prior to the start of the meal or 20 minutes after the start of the meal, and is compared with Humalog (n=779). In my review of the pooled data, I primarily present and summarize information from the 52-week dataset and highlight any relevant differences from the 26-week dataset where appropriate.

Safety data from Study ITSI was not integrated with the MDI studies because of differences in method of administration (CSII) and design (2-period crossover) and is therefore summarized separately. My review of hypoglycemia is also presented separately for studies ITRM and ITRN, in T1D and T2D respectively, due to differences in study populations.

8.2. Review of the Safety Database

8.2.1. Relevant characteristics of the safety population:

The demographic characteristics of the safety populations from the core clinical trials are shown in **Table 23**. Refer to discussion of individual trial results in **Section 6** of this for details of the respective trial population demographics.

Table 23: Summary of Demographics and Diabetes Characteristics Randomized Patients, Studies ITRM and ITRN

Parameter	Study ITRM (T1D)		Study ITRN (T2D)		Total		p-value ^a
	Humalog (N=442)	All LY (N=780)	Humalog (N=337)	All LY (N=336)	Humalog (N=779)	All LY (N=1116)	
Sex, n (%)							
Female	186 (42.1)	348 (44.6)	162 (48.1)	152 (45.2)	348 (44.7)	500 (44.8)	0.8214
Male	256 (57.9)	432 (55.4)	175 (51.9)	184 (54.8)	431 (55.3)	616 (55.2)	
Age (years)							
Mean (SD)	44.5(13.6)	44.3 (13.9)	61.0 (9.2)	60.2 (9.4)	51.6 (14.5)	49.1 (14.7)	0.4507
Minimum, Maximum	18, 78	18, 84	28, 84	34, 83	18, 84	18, 84	

Age Groups, n (%)							
<65 years	407 (92.1)	717 (91.9)	194 (57.6)	212 (63.1)	601 (77.2)	929 (83.2)	0.2575
>65 years	35 (7.9)	63 (8.1)	143 (42.4)	124 (36.9)	178 (22.8)	187 (16.8)	
<75 years	437 (98.9)	771 (98.8)	327 (97.0)	327 (97.3)	764 (98.1)	1098 (98.4)	0.8800
>75 years	5 (1.1)	9 (1.2)	10 (3.0)	9 (2.7)	15 (1.9)	18 (1.6)	
BMI (kg/m ²)							
Mean (SD)	26.4 (4.3)	26.6 (4.4)	32.4 (5.8)	32.1 (5.7)	29.0 (5.8)	28.3 (5.4)	0.8815
Minimum. Maximum	17, 42	16, 40	19, 45	20, 48	17, 45	16, 48	
Duration of Diabetes (years)							
Mean (SD)	19.1 (12.0)	18.8 (12.0)	16.6 (7.9)	16.4 (7.8)	18.0 (10.5)	18.1 (11.0)	0.5869
Minimum. Maximum	1, 59	1, 64	1, 40	2, 44	1, 59	1, 64	
HbA1c at Baseline (%)							
Mean (SD)	7.3 (0.7)	7.3 (0.6)	7.3 (0.7)	7.3 (0.7)	7.3 (0.7)	7.3 (0.7)	0.8263
Minimum. Maximum	6, 10	5, 10	5, 11	6, 9	5, 11	5, 10	
Basal Insulin at Baseline, n (%)							
Degludec	193 (43.8)	346 (44.4)	80 (23.7)	76 (22.6)	273 (35.1)	422 (37.8)	0.9833
Glargine	248 (56.2)	434 (55.6)	257 (76.3)	260 (77.4)	505 (64.9)	694 (62.2)	
Prandial Insulin Dosing Plan, n (%)							
Carbohydrate Counting	205 (46.4)	349 (44.7)	30 (8.9)	24 (7.1)	235 (30.2)	373 (33.4)	0.4039
Pattern Adjustment	237 (53.6)	431 (55.3)	307 (91.1)	312 (92.9)	544 (69.8)	743 (66.6)	

Source: Adapted from Table 2.7.4.4 Summary of Clinical Safety and the MAED Demographic Tool

ANOVA = analysis of variance; BMI = body mass index; CMH = Cochran-Mantel-Haenszel; HbA1c = hemoglobin A1c; N = number of patients in the analysis population; n = number of patients in the specified category; SD = standard deviation; T1D = type 1 diabetes; T2D = type 2 diabetes.

^a ANOVA model with terms of treatment and study for continuous variables; CMH test stratified by study for categorical variables

8.2.1. Overall Exposure

The safety population was defined as all randomized patients who received at least 1 dose of the investigational product or comparator. A summary of the size of the safety population and duration of exposure to study drug administered via MDI SC route during trials ITRM and ITRN is presented in **Table 24**. In the MDI trials, 1116 patients were exposed to LY90001 with a mean duration of exposure of 254.7 days.

During Study ITSI, 49 patients received LY90001 via CSII, with a mean duration of exposure of 41.7 days.

Table 24: Summary of Exposure to Investigational Product from Randomization to Week 52 All Randomized Patients Studies 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)

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≥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**

8.2.2. Adequacy of the safety database:

The safety database is adequate to meet ICH E1 guidelines and FDA Guidance for development of products to treat diabetes, with regard to both the size of the safety population and the extent of exposure to LY900014. The patient demographics and disease characteristics with reference to the U.S. target population were also adequate to support these clinical trials.

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 and datasets was adequate to support a meaningful safety review. Key safety findings were reproducible and confirmed using the submitted datasets. Minor differences in the safety data results between the Applicant’s summaries and those I created did not change the overall conclusions of the findings.

8.3.2. Categorization of Adverse Events

Safety measures 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.

Adverse events 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 21.0 and 21.1 lowest level term (LLT) was used in the treatment emergent assessment for 26 and 52 weeks, respectively. 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 for the integrated Phase 3 MDI studies. Study ITSI included the screening and

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lead-in periods for 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 or 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 8.5.1** for categorization of hypoglycemia.

8.3.3. Routine Clinical Tests

The schedule of study activities including routine clinical testing is summarized in **Table 43** and discussed in **Section 6.1.1** 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, 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.*

8.4. Safety Results

Overview

MDI Studies

An overview of AEs for patients in the safety population is provided in **Table 25**. The incidence of SAEs was statistically significantly lower in the All LY group compared to Humalog (Humalog 12.8%; All LY 10.1%; $p=0.030$). No significant treatment differences were noted in any other AE category. A total of six deaths were reported (Humalog 2; All LY 4).

Table 25: Overview of Adverse Events from Randomization to Safety Follow-up Safety Population Studies 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

CSII study

An overview of AEs for the safety population in Study ITSI is presented in **Table 26**. During the 6-week treatment periods, there were no deaths or discontinuations due to AEs. Two patients reported SAEs (LY900014, 1 [2.0%]; Humalog, 1 [2.1%]). The incidence of patients reporting at least 1 TEAE was statistically significantly higher for LY900014 compared to Humalog (LY900014 46.9%; Humalog 18.8%; p=0.015).

Reviewer comment: *The higher rate of TEAE with LY900014 in the CSII study was related to infusion site reactions and is discussed further in **Section 8.5.2**.*

Table 26: Overview of Adverse Events from Randomization to Week 6 of Each Randomized Treatment Period Safety Population Study ITSI

Adverse Events ^a	Humalog	LY900014	p-value ^b
	(N=48)	(N=49)	
	n (%)	n (%)	
Deaths	0	0	
Serious Adverse Events	1 (2.1)	1 (2.0)	1.000
Discontinuation from Study due to an Adverse Event	0	0	
Treatment-Emergent Adverse Events	9 (18.8)	23 (46.9)	0.015
Treatment-Emergent Adverse Events Related to Study Drug ^c	6 (12.5)	13 (26.5)	0.210

Abbreviations: N = number of patients in the analysis population; n = number of patients with events meeting specified criteria.

a Patients may be counted in more than one category.

b p-values for comparisons between LY900014 and Humalog were computed using Prescott's Exact test.

c Includes events that were considered related to study treatment as judged by the investigator.

Source: Summary of Clinical Safety Table 2.7.4.10

8.4.1. Deaths

MDI studies

In the Phase 3 studies from randomization to safety follow-up and prior to database lock, six deaths (All LY, 4; Humalog, 2) occurred. Four additional deaths (All LY, 3; Humalog, 1) were reported after the safety follow-up visit, all occurring greater than 45 days after study drug discontinuation and therefore unlikely to be related to IP. Brief clinical summaries of the six deaths occurring prior to the database lock and safety follow-up visit are provided below.

- Patient (b) (6) (LY900014), a 57-year old male with T1D, reported an SAE of *colon cancer* approximately 4 months after starting study treatment. Study treatment was discontinued due to the AE, and the patient died approximately 4 months later.
- Patient (b) (6) (Humalog), a 67-year old male with T1D, experienced an SAE of *aortic stenosis* approximately 3 months after starting study treatment. Study treatment was discontinued due to the AE, and the patient died approximately 1 month later.
- Patient (b) (6) (LY+20), a 61-year old male with T1D, was found dead in a river after days of torrential rains approximately 8.5 months after starting treatment. No autopsy was performed. Based on the patient's clinical history in managing hypoglycemia and never having been transferred for treatment of severe hypoglycemia, the investigator did not believe the death was related to hypoglycemia or study treatment.
- Patient (b) (6) (LY900014), a 70-year old male with T2D, experienced SAEs of *peripheral vascular disorder, acute kidney injury, acute respiratory failure, septic shock, and pneumonia* approximately 4.5 months after starting study treatment. Study treatment was discontinued due to the AEs, and the patient died 2 days later.
- Patient (b) (6) (Humalog), a 63-year old female with T2D, experienced an SAE of *sudden death* approximately 4 months after starting study treatment.

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- Patient (b) (6) (LY900014), a 68-year old female with T2D, experienced an SAE of *acute myocardial infarction* approximately 3.5 months after starting study treatment. She died on the same day.

Reviewer comment: I reviewed the case narratives of the deaths. Case (b) (6) involved a drowning under unusual circumstances, and therefore hypoglycemia cannot definitively be ruled out as cause of the fatality. Case (b) (6) involved the unwitnessed sudden death of a patient who lived alone with co-morbidities of hypertension, asthma, chronic kidney disease, and hepatic steatosis. Case (b) (6) involved a man with preexisting peripheral vascular disease, cardiovascular disease who developed a foot ulcer which lead to osteomyelitis prior to diagnosis with sepsis. I agree with the investigators' assessments that the deaths in these and the other cited cases were unlikely related to IP.

8.4.2. Serious Adverse Events (nonfatal)

MDI:

The SAE profile from randomization to safety follow-up by preferred term (PT) reported by more than 1 patient is summarized in **Table 27**.

The percentage of patients reporting at least 1 SAE was nominally statistically higher in the Humalog group (All LY 10.1%; Humalog 12.8% (p=0.03)) with no statistically significant treatment differences noted at the PT level. The most frequently reported SAEs (≥3 All LY patients) were *hypoglycaemia, pneumonia, cellulitis, angina pectoris, chronic obstructive pulmonary disease, and nephrolithiasis*. In the individual studies, the most frequent system organ class (SOC) of SAEs reported was Metabolism and Nutrition Disorders in Study ITRM, and Infections and Infestations in Study ITRN.

Per study protocols, events of severe hypoglycemia were to be reported as SAEs in all studies. At times, investigators reported severe hypoglycemia using specific neuroglycopenic PT (i.e., *hypoglycaemic coma, hypoglycaemic unconsciousness*), but not in most cases. The incidence of all hypoglycemic events recorded as SAEs is similar between treatment arms and is discussed in greater detail in **Section 8.5.1**.

Table 27: Serious Adverse Events by Preferred Term Reported by >1 Patient from Randomization to Safety Follow-up Safety Population Studies ITRM and ITRN

Preferred Term	Humalog (N=779)	All LY (N=1116)	Total (N=1895)	OR ^a	Heterogeneity	
	n (%)	n (%)	n (%)		p-value ^b	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

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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

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 with events meeting specified criteria; NC = not calculable; OR = odds ratio; SAE = serious adverse event.

a Mantel-Haenszel Odds Ratio stratified by study. All LY is numerator.

b Heterogeneity of odds ratios across studies was assessed using the Breslow Day test.

c p-values are from Cochran-Mantel-Haenszel (CMH) test of general association stratified by study.

Source: Summary of Clinical Safety Table 2.7.4.14

CSII

In the CSII dataset, the only SAE reported was *hypoglycaemia*, reported by two patients (LY, 1; Humalog, 1).

Reviewer Comment: *No significant imbalances are noted between treatment groups with respect to SAEs. When comparing differences between T1D and T2D study populations, the most frequent SAEs reported in the T1D population were related to hypoglycemia. In contrast, patients with T2D had SAE reports most frequently related to infections.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

MDI:

Patients in Studies ITRM and ITRN who discontinued the study for any reason also stopped study drug if the discontinuation occurred prior to or at the 26-week (Studies ITRM and ITRN) or 52-week (Study ITRM) visit. However, patients who discontinued study drug were encouraged to remain in the study for continued safety monitoring. Patients may have subsequently discontinued the study for the same or a different reason than the reason for stopping the study drug.

Table 28 summarizes the AEs leading to discontinuation of IP from randomization to Week 52 safety follow-up. The frequency of patients with at least 1 AE leading to discontinuation of IP was similar between treatment groups (All LY 1.7%; Humalog 1.0%). The only AE reported by more than 1 patient as the reason for discontinuation of IP was *maternal exposure before pregnancy*.

Table 28: Adverse Events Reported as Reason for Discontinuation from IP Preferred Term by Decreasing Frequency from Randomization to Week 52 Safety Population Studies ITRM and ITRN

Preferred Term	n	Humalog (N=779) (%)	n	All LY (N=1116) (%)	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

CSII: No IP discontinuations occurred due to AEs during Study ITSI.

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Reviewer comment: Overall, study participants tolerated the use of IP in the Phase 3 studies, with fewer than 2% of patients discontinuing IP due to AE.

8.4.4. Significant Adverse Events

The Applicant did not classify any AEs as significant adverse events except those leading to discontinuation from study or study drug. See **Section 8.5** for discussion on Submission-Specific Safety Issues.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

MDI:

The proportion of patients reporting at least one TEAE was similar in both treatment arms (All LY 63.1%; Humalog 63.3%). The most frequent SOCs of TEAEs reported in All LY-treated patients included Infections and Infestations (All LY, 39.5%; Humalog, 39.0%); Musculoskeletal and Connective Tissues Disorders (All LY, 11.1%; Humalog, 11.7%); and Gastrointestinal Disorders (All LY, 10.3%; Humalog, 9.8%). **Table 29** summarizes the most frequent AEs occurring in greater than 2% of the safety population.

The only SOC with an unfavorable statistically significant treatment difference for All-LY reported in at least 5% of patients was the General Disorders and Administration Site Conditions (All LY, 7.0%; Humalog, 3.7% (p=0.001)). This finding was driven by the PTs *pyrexia*, *injection site pain*, and *injection site reaction*. The AE of injection site reaction is discussed in greater detail in **Section 8.5.1.2** as a submission specific safety issue.

Treatment-emergent adverse events reported in at least 5% of All LY-treated patients included *nasopharyngitis* (All LY, 16.0%; Humalog, 14.6%) and *upper respiratory tract infection* (All LY, 6.0%; Humalog, 6.4%).

CSII

The proportion of patients reporting at least 1 TEAE was statistically significantly higher for LY900014 (LY 46.9%; Humalog 18.8% (p=0.015)). Similar to the MDI studies, SOC with an unfavorable statistically significant treatment difference for LY900014 reported in at least 5% of patients was the General Disorders and Administration Site Conditions (LY900014 38.8%; Humalog, 12.5% (p=0.006)). This finding was driven by the PTs *infusion site pain* (LY900014 18.4%; Humalog 4.2%) and *infusion site reaction* (LY 18.4%, Humalog 8.3%) (see **Table 30**). See further discussion of AEs related to infusion site reaction in **Section 8.5.1.2**.

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Table 29: Treatment Emergent Adverse Events Occurring in at Least 2% of Patients from Randomization to Week 52 Safety Population Studies ITRM and ITRN

System Organ Class	Preferred Term	All LY		HUMALOG	
		Column %	n	Column %	n
Infections and infestations	Bronchitis	4.49%	30	5.94%	28
	Gastroenteritis	2.99%	20	3.40%	16
	Influenza	7.78%	52	8.49%	40
	Nasopharyngitis	33.08%	221	29.72%	140
	Sinusitis	3.29%	22	3.82%	18
	Upper respiratory tract infection	11.38%	76	12.53%	59
	Urinary tract infection	3.89%	26	3.82%	18
Gastrointestinal disorders	Diarrhoea	3.59%	24	2.97%	14
	Vomiting	2.84%	19	2.34%	11
General disorders and administration site conditions	Injection site pain	2.69%	18	0.00%	0
	Injection site reaction	2.99%	20	0.21%	1
Musculoskeletal and connective tissue disorders	Arthralgia	4.19%	28	2.76%	13
	Back pain	4.04%	27	4.25%	20
Metabolism and nutrition disorders	Hypoglycaemia	9.13%	61	15.50%	73
Vascular disorders	Hypertension	3.59%	24	4.25%	20

Source: Created by reviewer using JMP15 with ADAE.xpt data sets

Table 30: Treatment-Emergent Adverse Events by PT by Decreasing Frequency within SOC From Randomization to Week 6 of Each Randomized Treatment Period Safety Study ITSI

System Organ Class Preferred Term	Humalog (N=48)		LY900014 (N=49)		Total (N=49)		p-value* ^a
	n	(%)	n	(%)	n	(%)	
Subjects with >= 1 TEAE	9	(18.8)	23	(46.9)	26	(53.1)	0.015
General disorders and administration site conditions	6	(12.5)	19	(38.8)	21	(42.9)	0.006
Infusion site pain	2	(4.2)	9	(18.4)	11	(22.4)	0.095
Infusion site reaction	4	(8.3)	9	(18.4)	10	(20.4)	0.415
Infusion site erythema	0	(0.0)	2	(4.1)	2	(4.1)	0.490
Infusion site pruritus	0	(0.0)	1	(2.0)	1	(2.0)	1.000
Metabolism and nutrition disorders	1	(2.1)	2	(4.1)	3	(6.1)	1.000
Hyperglycaemia	0	(0.0)	1	(2.0)	1	(2.0)	1.000
Hypoglycaemia	1	(2.1)	1	(2.0)	2	(4.1)	1.000
Musculoskeletal and connective tissue disorders	0	(0.0)	2	(4.1)	2	(4.1)	0.479
Arthralgia	0	(0.0)	1	(2.0)	1	(2.0)	0.479
Arthritis	0	(0.0)	1	(2.0)	1	(2.0)	
Infections and infestations	2	(4.2)	1	(2.0)	3	(6.1)	0.601
Tooth infection	0	(0.0)	1	(2.0)	1	(2.0)	1.000
Nasopharyngitis	1	(2.1)	0	(0.0)	1	(2.0)	0.479
Sinusitis	1	(2.1)	0	(0.0)	1	(2.0)	0.479
Injury, poisoning and procedural complications	0	(0.0)	1	(2.0)	1	(2.0)	0.479
Muscle injury	0	(0.0)	1	(2.0)	1	(2.0)	0.479
Respiratory, thoracic and mediastinal disorders	0	(0.0)	1	(2.0)	1	(2.0)	1.000
Catarrh	0	(0.0)	1	(2.0)	1	(2.0)	1.000

Abbreviations: IP = investigational product; N = number of subjects in the analysis population; n = number of subjects with at least one event meeting the specified criteria; TEAE = Treatment-Emergent Adverse Event.

*a - p-values for comparisons between LY900014 and Humalog were computed using Prescott's Exact test.

Source CSR Study ITSI Table ITSI.14.150.

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Reviewer comment: The TEAEs reported in the MDI were similar between LY900014 and Humalog. An imbalance in ‘arthralgia’ not favoring LY900014 is noted, the reason for this finding is unclear; however, the reported incidence is low. Overall, the safety profile of LY900014 appears to be similar to Humalog with the exception of greater incidence of injection site reactions, which should be noted in the labeling in Section 6.1 Clinical Trials Experience.

8.4.6. Laboratory Findings

In all Phase 3 studies, there were no statistically significant treatment differences in the incidence of treatment-emergent abnormal laboratory values.

8.4.7. Vital Signs

MDI

In the MDI studies, there was no statistically significant treatment differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse or weight. Mean weight in both treatment groups increased at 26 weeks (All LY, 0.9 kg; Humalog, 1.1 kg) and was minimally greater at 52 weeks (All LY, 1.1 kg; Humalog, 1.2 kg). **Table 31** presents a summary and analysis of changes in vital signs for the MDI studies from randomization to Week 26 for the safety population.

Table 31: Summary and Analysis of Vital Signs and Weight from Randomization to Week 26 Analysis of Covariance Safety Population, Studies ITRM and ITRN

Variable Time Point	Humalog (N=778) LSM (SE)	All LY (N=1113) LSM (SE)	LSM Difference ^{a, b}	p-value ^{a, b}
Systolic Blood Pressure (mm Hg)				
Baseline	127.8 (0.55)	126.2 (0.46)	-1.6	0.023
LOCF endpoint	125.1 (0.43)	126.0 (0.36)	0.9	0.122
Change from baseline	-1.8 (0.43)	-0.9 (0.36)	0.9	
Diastolic Blood Pressure (mm Hg)				
Baseline	75.3 (0.34)	75.6 (0.28)	0.3	0.524
LOCF endpoint	74.7 (0.28)	74.9 (0.24)	0.2	0.509
Change from baseline	-0.8 (0.28)	-0.6 (0.24)	0.2	
Pulse (bpm)				
Baseline	75.4 (0.38)	75.7 (0.32)	0.3	0.606
LOCF endpoint	75.6 (0.30)	75.5 (0.25)	-0.1	0.829
Change from baseline	0.0 (0.30)	0.0 (0.25)	-0.1	
Body weight (kg)				
Baseline	82.8 (0.68)	81.2 (0.57)	-1.6	0.072
LOCF endpoint	82.9 (0.10)	82.7 (0.09)	-0.2	0.135
Change from baseline	1.1 (0.10)	0.9 (0.09)	-0.2	

Abbreviations: All LY = LY900014 administered 0-2 minutes prior to the start of the meal or administered immediately after completion of a meal or at 20 minutes after the start of a meal; bpm = beats per minute; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the population with baseline and

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post-baseline values at the specified time point; SE = standard error.

a ANCOVA model for endpoint measures: Variable = Baseline + [Strata +] Treatment (Type III sum of squares).

b ANOVA model for baseline measures: Variable = Treatment (Type III sum of squares).

Source: Summary of Clinical Safety Table 2.7.4.36.

CSII

Table 32 presents a summary and analysis of changes in vital signs for each 6-week treatment period for Study ITSI. There was a statistically significantly greater increase in DBP from baseline to Week 6 for LY900014 compared with Humalog (LY900014, 2.5 mm Hg; Humalog, 0.1 mm Hg; $p=0.038$). There were no statistically significant treatment differences from baseline to Week 6 for SBP, pulse, or weight. In addition, there were no statistically significant treatment differences in the proportion of patients with treatment-emergent high or low vital signs or body weight.

Table 32: Summary and Analysis of Vital Signs and Weight from Randomization to Week 6 of Each Randomized Treatment Period Mixed Model Repeated Measures Safety Population, Study ITSI

Time Point	Treatment	N	Mean (SD)	LSM (SE)	LSM Difference (95% CI)	p-value ^a
Systolic Blood Pressure (mmHg)						
Week 0 (Baseline)	Humalog	48	122.6 (10.97)			
	LY900014	49	122.7 (10.87)			
Week 6	Humalog	47	123.6 (13.42)	123.6 (1.68)	1.3 (-1.9, 4.6)	0.408
	LY900014	47	125.0 (12.41)	124.9 (1.69)		
Diastolic Blood Pressure (mmHg)						
Week 0 (Baseline)	Humalog	48	74.3 (8.46)			
	LY900014	49	74.3 (8.37)			
Week 6	Humalog	47	74.4 (8.02)	74.4 (1.03)	2.4 (0.1, 4.7)	0.038
	LY900014	47	76.9 (8.45)	76.8 (1.03)		
Pulse (beats/min)						
Week 0 (Baseline)	Humalog	48	75.9 (10.68)			
	LY900014	49	75.9 (10.57)			
Week 6	Humalog	47	74.9 (11.83)	75.0 (1.17)	2.6 (-0.1, 5.4)	0.056
	LY900014	47	77.5 (11.12)	77.7 (1.16)		
Weight (kg)						
Week 0 (Baseline)	Humalog	48	76.6 (14.76)			
	LY900014	49	76.9 (14.75)			
Week 6	Humalog	47	77.4 (15.05)	77.3 (0.27)	-0.3 (-0.7, 0.1)	0.110
	LY900014	47	76.5 (14.71)	77.0 (0.27)		
Abbreviations: CI = confidence interval; LSM = least squares mean; MMRM = mixed model repeated measures; N = number of patients in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.						
^a MMRM model for post-baseline measures: Variable = Baseline + Period + Sequence + Strata + Time + Treatment*Time + Treatment (Type III sum of squares). Variance-Covariance structure = unstructured.						

Source: Summary of Clinical Safety Table 2.7.4.37.

Reviewer comment: Weight gain is an expected finding with all insulin products, particularly following dose titration to improve glycemic control. No treatment differences were noted for weight, SBP, or pulse. It is not clear why an isolated increase in DBP was observed following 6

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weeks of LY900014 exposure in the CSII study. No difference was noted in the MDI studies. Nevertheless, the modest increase of 2.5 mm Hg is not clinically significant.

8.4.8. **Electrocardiograms (ECGs)**

ECGs were obtained at baseline and were not routinely reassessed in Phase 3 studies.

8.4.9. **QT**

QT assessment did not occur during Phase 3 studies.

8.4.10. **Immunogenicity**

Development of antibodies with any new insulin therapy may potentially lead to reduced drug exposure and affect glycemic efficacy by neutralizing the effect of the drug, and sometimes may lead to requiring higher insulin doses to maintain glycemic control.

Blood samples for immunogenicity testing were collected, using a validated radioligand-binding assay, to determine antibody production against insulin lispro for all enrolled patients at baseline (Visit 2) prior to the first dose of study provided prandial insulin treatment. Treatment-emergent anti-insulin lispro antibodies (TEADA) were defined as anti-lispro antibodies present following study drug administration.

The TEADA was based on the change from baseline (Visit 2) to postbaseline (post-Visit 2) in the anti-insulin lispro antibody level (percent binding). TEADA could be sub-classified as either treatment-induced (not detected anti-insulin lispro antibody at baseline) or treatment-boostered (detected anti-insulin antibody at baseline). Treatment-induced response is a change from not detected anti-insulin lispro at baseline to postbaseline detected anti-insulin lispro. Treatment-boostered response is a change from detected anti-insulin lispro at baseline to postbaseline detected anti-insulin lispro antibody level of at least 157% of the baseline value.

Patients who completed the 4-week safety follow-up visit (Visit 801) and had TEADA that had not returned to baseline range were asked to participate in follow-up to monitor antibody levels. In addition to assessing TEADA status, subgroup analyses for the following selected efficacy and safety variables was performed by the TEADA status during the analysis period of Visit 2 to Visit 801: HbA1c and change from baseline in HbA1c; treatment-emergent injection site reaction and hypersensitivity reaction.

TEADA Status

In Study ITRM at baseline, there were a similar number of patients with detectable ADA in each treatment group (Humalog, 44%; LY900014, 47.8%). As summarize in **Table 33**, a similar

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proportion of those with detectable antibodies at baseline were cross reactive to native insulin (Humalog, 88.7%; LY900014, 90.7%).

Although at earlier timepoints (week 0 and 12) there were more TEADA patients in the Humalog group versus LY900014 group, and at later timepoints (week 52) more in the LY900014 group than Humalog group, overall, there were similar proportions of patients in the LY900014 and Humalog groups with TEADA (Humalog, 34.2%; LY900014, 37.3%). There were no statistically significant treatment differences in the number of patients with treatment-induced, treatment-boosted, or antibodies cross-reactive to native insulin, as summarized in **Table 34**. For patients with TEADA in both treatment groups, the antibody percent binding mean values remained low throughout the lead-in period and 52-week treatment period as depicted in **Figure 15**.

Table 33: Summary of Baseline Anti-Insulin Lispro Antibody Safety Population for the Double-Blind Treatment Groups I8B-MC-ITRM

	Humalog (N = 442) n (%)	LY900014 (N = 451) n (%)	Total (N = 893) n (%)	P-values* ^a Overall
Number of Patients	441	450	891	
Number of Patients with Detected Anti-Insulin Lispro Antibody (%)	195 (44.2)	215 (47.8)	410 (46.0)	0.313
Anti-Insulin Lispro Antibody Percent Binding (Detected Anti-Insulin Lispro Antibody)				
Mean	1.85	1.84	1.84	
Standard Deviation	2.56	3.01	2.80	
Median	0.92	0.89	0.92	
Minimum	0.41	0.41	0.41	
Maximum	17.22	34.67	34.67	
Number of Patients with Cross-Reactivity (%)	173 (88.7)	195 (90.7)	368 (89.8)	0.519
Cross-Reactivity Antibody Percent Binding (Cross Reactive Antibody)				
Mean	1.92	1.86	1.89	
Standard Deviation	2.62	3.91	3.36	
Median	1.00	0.88	0.93	
Minimum	0.25	0.25	0.25	
Maximum	15.99	49.79	49.79	

Abbreviations: N = number of subjects in population; n = number of subjects; Trt A = Humalog; Trt B = LY900014; Trt C = LY900014 Postmeal.

*a - P-values are based on Fisher's exact test.

Note 1: Only the TEADA evaluable patients defined as patients with baseline and at least one post-baseline measurement were included in this analysis.

Note 2: The percentage of cross-reactivity used the number of patients with detected anti-insulin lispro antibody as the denominator **Source: CSR Study ITRM 52-week Table ITRM 14.158.**

Table 34: Summary of Treatment-Emergent Anti-Insulin Lispro Antibody from Study Entry to Safety Follow-up Safety Population for the Double-Blind Treatment Groups Study ITRM

	Humalog	LY900014	Total	Pairwise p-values *a Humalog vs LY900014
Overall* ^b				
Number of Subjects	441	450	891	
Number of Subjects with TEADA (%)	151 (34.2)	168 (37.3)	319 (35.8)	0.364
Number of Subjects with Positive Cross-Reactivity (%)	119 (78.8)	131 (78.0)	250 (78.4)	0.892
Number of Subjects Return to Baseline Level (%) ^{*c}	99 (65.6)	102 (60.7)	201 (63.0)	0.417
Number of Subjects with Treatment Induced ADA (%)	88 (20.0)	99 (22.0)	187 (21.0)	0.460
Number of Subjects with Treatment Boosted ADA (%)	63 (14.3)	69 (15.3)	132 (14.8)	0.706

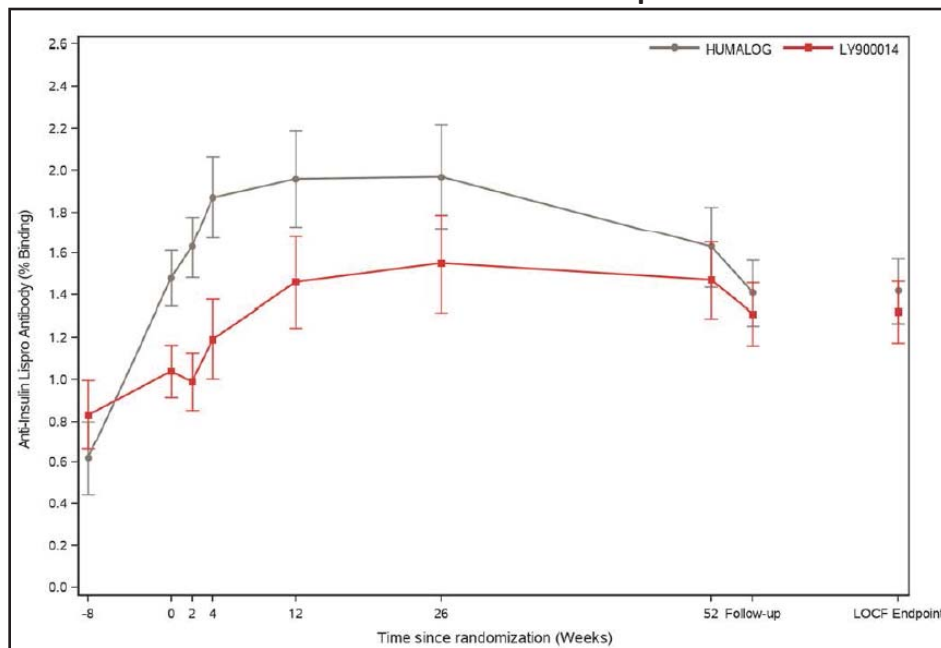
Abbreviations: ADA = anti-insulin lispro antibody; TEADA = treatment-emergent anti-insulin lispro antibody.

*a - p-value for treatment comparison from Fisher's exact test.

*b - Overall is defined as from Week 0 (Visit 8) to Safety Follow-up (Visit 801).

*c - Return to baseline at last visit is defined as anti-insulin lispro antibody no longer meeting TEADA criteria for Visit 801 result. **Source: CSR Study ITRM 52-week Table ITRM 12.22.**

Figure 15: Anti-insulin Lispro Antibody (mean percent binding) from Lead-in to Safety Follow-up for TEADA Patients in the Double-Blind Treatment Groups.



Abbreviation: LOCF=last observation carried forward; LSM=least squares mean; SE = standard error; TEADA = treatment-emergent anti-insulin lispro antibodies.

Data are LSM (SE) **Source: CSR Study ITRM 52-week Table ITRM.12.7.**

TEADA Follow-up

Patients in who developed TEADA at any time during the study that had not returned to baseline by the completion of the 4-week safety follow-up (Visit 801) continued to have insulin lispro antibody levels monitored for up to 26 weeks after Visit 801. A total of 147 patients in Study ITRM met the criteria. Overall, the number of patients with TEADA decreased throughout the follow-up period: visit 801 (147 patients), visit 802 (74 patients), visit 803 (26 patients). Patients were evenly distributed across both treatment groups. The ADA percent binding values

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were also numerically very similar between patients in the LY900014 treatment groups compared to Humalog

Subgroup analyses by TEADA Status

The subgroup analyses of TEADA status revealed no clinical impact on selected efficacy and safety variables.

In terms of efficacy, there was no apparent correlation noted between HbA1c levels and anti-lispro percent binding in any treatment group, nor any correlations between total daily insulin dose and anti-insulin lispro percent binding in any treatment group.

In terms of safety, there were no statistically significant treatment-by-TEADA interactions during the treatment period of 0 to 26 weeks, indicating no differential treatment effect on overall hypoglycemia rate for patients with or without TEADA. Due to the small number of patients with events, the logistic regression model used for the analysis of potential systemic hypersensitivity reactions and potential injection site reactions at 52 weeks did not converge; therefore, the treatment-by-TEADA status interaction could not be assessed. Treatment-emergent systemic hypersensitivity reactions (narrow) were reported by patients with TEADA (LY900014, 8 [5.0%]; Humalog, 2 [1.4%]) and patients without TEADA (LY900014, 9 [3.1%]; Humalog, 14 [4.8%]). Treatment-emergent injection site reactions (narrow) were reported by patients with TEADA (LY900014, 6 [3.7%]; Humalog, 0) and patients without TEADA (LY900014, 9 [3.1%]; Humalog, 4 [1.4%]).

Reviewer comment: *Although there were instances of treatment-induced and treatment-boosted TEADA during the study, there appear to be no associated adverse clinical sequelae such as loss of efficacy or increased safety risk. In general, the immunogenicity safety profile for LY900014 appears to be similar to Humalog.*

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hypoglycemia

During study participation, patients were encouraged to perform SMBG whenever hypoglycemia was suspected, either by symptoms experienced or perceived increased risk as related to dietary intake, physical activity, or inadvertent or atypical insulin dosing. All patients were instructed to treat a BG $\leq$ 70 mg/dL as hypoglycemia. Hypoglycemia events were collected in eCOA. If a hypoglycemia event was suspected, the patient was to record the BG value, any associated symptoms, and the treatment administered in eCOA. The patient was to contact the site as necessary. Reports of hypoglycemia were classified by the investigator as “severe” or “not severe,” based upon data collected in eCOA and in consultation with the patient. All episodes of severe hypoglycemia were reported as AEs via electronic data entry and as SAEs.

Hypoglycemia was described using the following definitions in the clinical study reports:

- Documented Glucose Alert (BG $\leq$ 70 mg/dL):
 - Documented symptomatic hypoglycemia: an event with typical symptoms of hypoglycemia.
 - Documented asymptomatic hypoglycemia: an event without typical symptoms of hypoglycemia.
 - Documented unspecified hypoglycemia: with no information about symptoms of hypoglycemia available (also called unclassifiable hypoglycemia).
- Documented Clinically Significant Hypoglycemia (with similar criterion as above, except for threshold BG $<$ 54 mg/dL):
 - Documented symptomatic hypoglycemia
 - Documented asymptomatic hypoglycemia
 - Documented unspecified hypoglycemia
- Severe Hypoglycemia: during these episodes, patients have an altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and the event requires the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG $\leq$ 70 mg/dL).
- Other Hypoglycemia:
 - Nocturnal Hypoglycemia: any documented hypoglycemic event (including severe hypoglycemia) that occurs between bedtime and waking.
 - Probable Symptomatic Hypoglycemia: an event during which symptoms are present, but BG measurement was not reported.
 - Overall (or Total) Hypoglycemia: this category 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.

Due to the disparity in the rate and incidence of hypoglycemia in T1D and T2D populations, the study results of ITRM and ITRN are presented separately. For Study ITRM, I discuss the results of the 26-week study, rather than the 52-week study, as this includes data from the LY+20 treatment arm, allowing comparison to pre-meal dosing regimens of Humalog and LY900014. As the findings of the 52-week study are generally similar, my review only highlights any significant differences which were noted. For my review of safety, I primarily focus on the incidences and rates of severe hypoglycemia and documented clinically significant

hypoglycemia of < 54 mg/dL with and without symptoms. Additional review of the postmeal hypoglycemia patterns are presented since LY900014 is used as prandial therapy.

8.5.1.1. Study ITRM

Severe Hypoglycemia

Table 35 summarizes the rate and incidence of severe hypoglycemia from Study ITRM.

Incidence: There was no statistically significant difference between treatment arms in the incidence of severe hypoglycemia from randomization to Week 26: LY900014, n=25 (5.5%); Humalog, n=25 (5.7%); LY+20, n=15 (4.6%).

Rate: There was no significant difference in the rate of severe hypoglycemia between treatment groups.

The incidence and rate of severe hypoglycemia were numerically lower for both LY900014 and LY+20 in comparison to Humalog. There was also no statistically significant difference in the rate or incidence of severe postmeal hypoglycemia.

Table 35: Summary of Severe Hypoglycemia Rate and Incidence from Randomization to Week 26 Prior to Discontinuation of Study Drug Study ITRM Safety Population

Treatment	Rate					Incidence		
	Mean (SD)	Aggregate Rate/100 Years	p-value ^a		p-value ^a (%)	Episodes	p-value ^b	
			vs Humalog	vs LY900014			vs Humalog	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

Documented Hypoglycemia BG < 54 mg/dL

Figure 16 illustrates the rate and incidence for each category and subcategory of hypoglycemia (BG <54 mg/dL) at baseline and for the 26-week treatment period, prior to discontinuation of study drug.

Incidence: There were no statistically significant treatment differences (LY900014 versus Humalog, LY+20 versus Humalog, LY+20 versus LY900014) in incidence of documented hypoglycemia <54 mg/dL in any subcategory.

Rate:

- There were no statistically significant treatment differences (LY900014 versus Humalog, LY+20 versus Humalog, LY+20 versus LY900014) in the rate of all documented hypoglycemia, documented symptomatic hypoglycemia, or nocturnal hypoglycemia.

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- There was a statistically significantly higher rate of non-nocturnal hypoglycemia and all documented hypoglycemia in the LY+20 group compared to LY900014; however, these differences were present at baseline.

Postmeal Hypoglycemia

Figure 17 illustrates the rate and incidence of documented symptomatic and asymptomatic postmeal hypoglycemia with BG <54 mg/dL by postmeal time interval for the 26-week treatment period.

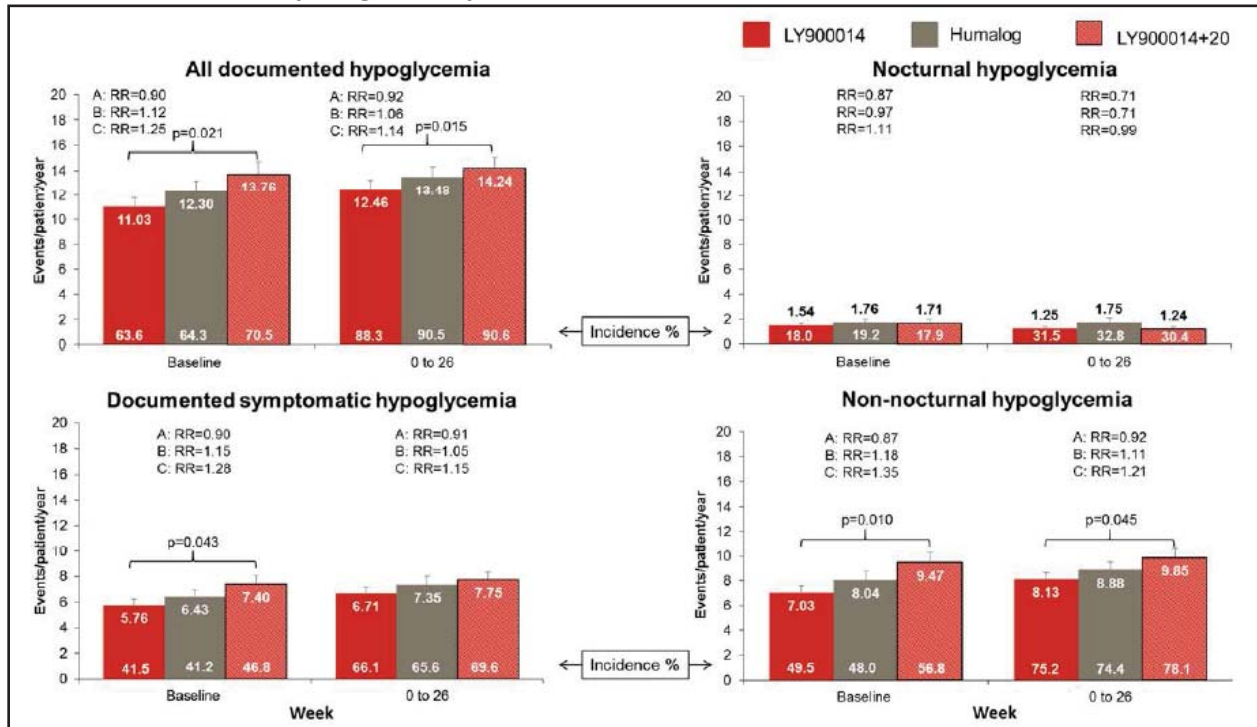
Incidence: There were no statistically significant treatment differences (LY900014 versus Humalog, LY+20 versus Humalog, LY+20 versus LY900014) in the incidence of symptomatic and asymptomatic hypoglycemia of < 54 mg/dL at any postmeal time point.

Rate:

- There were no statistically significant treatment differences (LY900014 versus Humalog, LY+20 versus Humalog, LY+20 versus LY900014) in the rate for ≤ 0.5 , ≤ 1 , ≤ 2 , ≤ 4 , >1 to ≤ 2 , and >2 to ≤ 4 hours postmeal.
- More than 4 hours postmeal, the rate was statistically significantly lower in the LY900014 group compared with the Humalog group with RR (95% CI) of 0.62 (0.47, 0.83) $p=0.001$.
- The rate of hypoglycemia more than 4 hours postmeal for the LY+20 group was numerically lower compared to the Humalog group, but statistically significantly higher compared to LY900014 group with RR (95%) of 1.43 (1.11, 1.85) $P=0.006$.

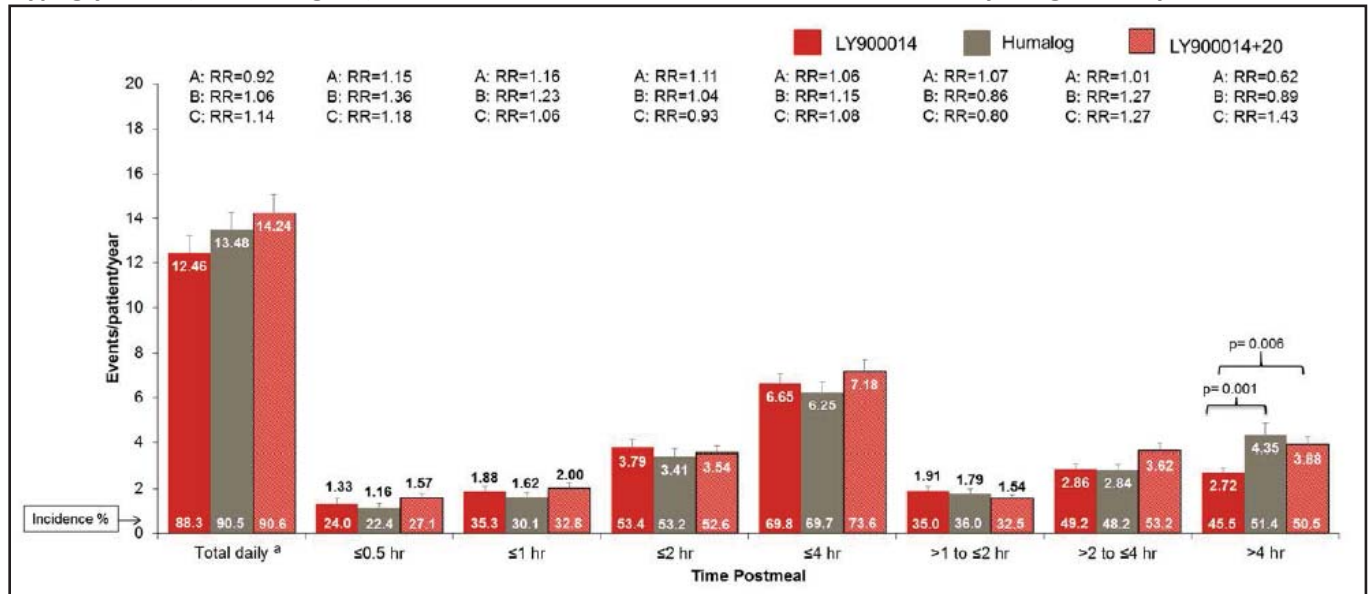
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Figure 16 : Rate of Hypoglycemia (BG <54 mg/dL) at Baseline and 0 to 26 Weeks Prior to Discontinuation of Study Drug in Study ITRM



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 17: Rate and Incidence of Documented Symptomatic and Asymptomatic Postmeal Hypoglycemia (BG <54 mg/dL) from Week 0 - 26 Prior to Discontinuation of Study Drug in Study 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**

Hypoglycemia by CGM

Study ITRM included a blinded CGM sub-study. Data from the CGM participants revealed that statistically significantly less time was observed in hypoglycemic range (<50 mg/dL) at Week 26 for the LY900014 and LY+20 groups versus Humalog.

- LY900014 versus Humalog showed 5.6 minutes less time in hypoglycemia (p=0.023) during nighttime with no other differences for daytime or the 24-hour periods.
- LY+20 versus Humalog showed 9.4 minutes less time in hypoglycemia (p=0.010) during daytime and 5.4 minutes less time in hypoglycemia (p=0.043) during nighttime and 14.3 minutes less time in hypoglycemia (p=0.010) for the 24-hour period.
- LY+20 versus LY900014 showed no statistically significant treatment differences for any period.

Reviewer comment: The hypoglycemia data from Study ITRM in patients with T1D show that LY900014 has a comparable safety profile to Humalog in with respect to postprandial hypoglycemia and may offer the advantage in terms of reducing risk of hypoglycemia between meals (>4 hours post injection).

- The rate and incidence of both severe and clinically significant hypoglycemia of BG< 54 mg/dL for LY900014 is comparable to Humalog. There were no statistically significant differences in rate or incidence of these events found to be unfavorable for LY900014 or LY+20, in comparison to Humalog.

- *When LY900014 is given at mealtime, the rate of hypoglycemia > 4 hours postmeal is statistically significantly lower than Humalog. This finding results in a numerically lower rate of total daily hypoglycemia for mealtime LY900014 as well. Fewer between meal hypoglycemic events is what would be expected with a product with a faster time-action profile and shorter duration of action. In this study, postmeal hypoglycemia for mealtime LY900014 occurs at >1 to ≤2 hours timepoint at a numerically slightly higher rate than Humalog and LY+20.*
- *With LY+20, postmeal hypoglycemia occurs at a later timepoint of >2 to ≤4-hour at numerically higher rate than Humalog and mealtime LY900014. Given that the change in HbA1c for LY+20 at 26 weeks in ITRM was statistically significantly worse compared to Humalog, it is somewhat surprising that the total daily postmeal hypoglycemia rate for LY+20 is numerically modestly higher, not lower, than the other treatment arms.*
- *Mealtime LY900014 administration is associated with a more favorable profile than LY+20 in terms of hypoglycemia. Mealtime LY900014 is also superior to LY+20 in terms of efficacy.*

8.5.1.2. Study ITRN

Severe Hypoglycemia

Table 36 summarizes the rate and incidence of severe hypoglycemia from Study ITRN in which there were 9 patients with ≥1 event of severe hypoglycemia.

Incidence: There was no statistically significant difference between treatment arms in the incidence of severe hypoglycemia from randomization to Week 26: LY900014, n=3 (0.89%); Humalog, n=6 (1.8%).

Rate: There was no significant difference in the rate of severe hypoglycemia between treatment groups.

The incidence and rate of severe hypoglycemia were numerically lower for LY900014 in comparison to Humalog.

Table 36: Summary of Severe Hypoglycemia Rate and Incidence from Randomization to Week 26 Prior to Discontinuation of Study Drug Study ITRN Safety Population

Treatment	N	Mean (SD)	Rate		Incidence		
			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**

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Documented Hypoglycemia BG < 54 mg/dL

Table 37 Presents a summary and analysis of the rate alongside the incidence of hypoglycemia (BG <54 mg/dL) by subcategory for the safety population of Study ITRN.

Figure 18 illustrates the rate for each category and subcategory of hypoglycemia (BG <54 mg/dL) for the 26-week treatment period, prior to discontinuation of study drug.

Incidence: There were no statistically significant treatment differences in the incidence of hypoglycemia in any subcategory.

Rate: While no statistically significant treatment differences were noted in the rate of all documented hypoglycemia, a statistically significantly higher rate of symptomatic hypoglycemia was observed in the LY900014 group compared with the Humalog group with RR (95%) of 1.64 (1.14, 2.38) P=0.009.

I conducted a subgroup analysis of the study subjects with documented symptomatic hypoglycemia of BG<54 mg/dL to further evaluate the disparity in the incidence and rate of these events. I noted that the LY900014 group had 5 subjects with greater than 10 symptomatic hypoglycemic events (ranging from 11 to 30 events/patient) while the Humalog group had only one such subject (14 events/patient). Thus, 5 outliers in the LY900014 group comprised over 25% of the recorded events, driving the higher rate of symptomatic hypoglycemia in the LY900014 treatment arm.

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Table 37: Hypoglycemia Rate (Adjusted for 1 Year) and Incidence for Hypoglycemia < 54 mg/dL from Randomization to Week 26 Prior to Discontinuation of Study Drug Study ITRN Safety Population

Category/Subcategory of Hypoglycemia Treatment	N	Rate		Incidence		
		LSM (SE)	p-value ^a	n (%)	Episodes	p-value ^b
BG <54 mg/dL (3.0 mmol/L)						
Documented symptomatic						
Humalog	337	1.34 (0.16)	0.009	103 (30.56)	223	0.546
LY900014	336	2.21 (0.32)		110 (32.74)	369	
All documented						
Humalog	337	7.43 (0.56)	0.873	264 (78.34)	1243	0.268
LY900014	336	7.57 (0.66)		251 (74.70)	1257	
Non-nocturnal						
Humalog	337	3.20 (0.34)	0.166	168 (49.85)	534	0.512
LY900014	336	3.92 (0.40)		176 (52.38)	653	
Nocturnal						
Humalog	337	0.53 (0.09)	0.276	55 (16.32)	89	0.410
LY900014	336	0.68 (0.11)		63 (18.75)	113	

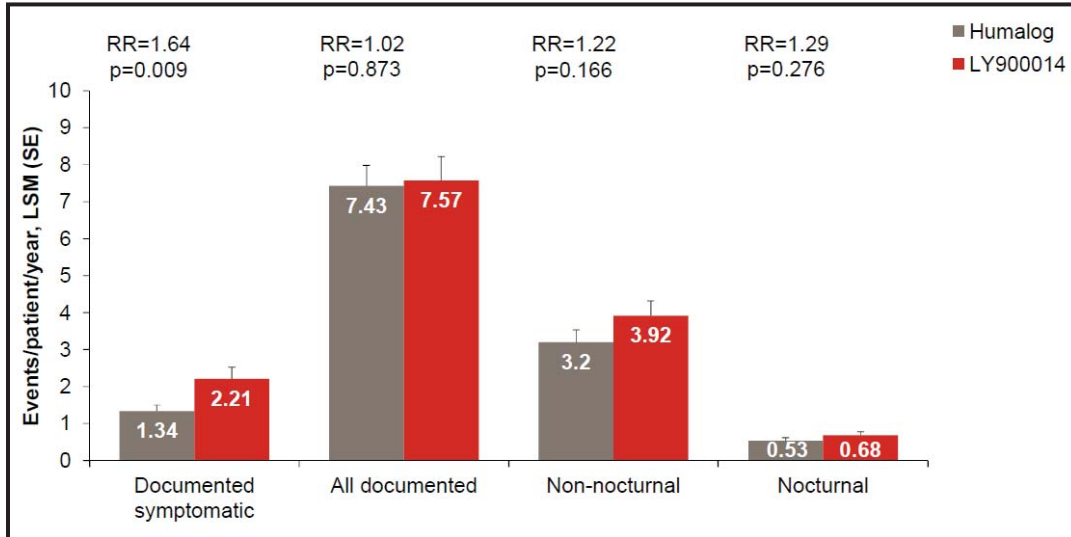
Abbreviations: BG = blood glucose; LSM = least squares mean; N = number of patients in the population with baseline and post-baseline value at the specified time point; n = number of patients with hypoglycemia; SE = standard error.

^a Negative binomial model for postbaseline comparisons between treatment and control groups: Number of episodes = Treatment with log (exposure in days/365.25) as an offset variable.

^b Logistic regressions model for postbaseline comparisons between treatment and control groups: Incidence = Treatment.

Source: Summary of Clinical Safety Table 2.7.4.25

Figure 18: Rate of Hypoglycemia from 0 to 26 weeks (BG<54 mg/dL) Prior to Discontinuation of Study Drug in Study 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

Postmeal Hypoglycemia

Incidence:

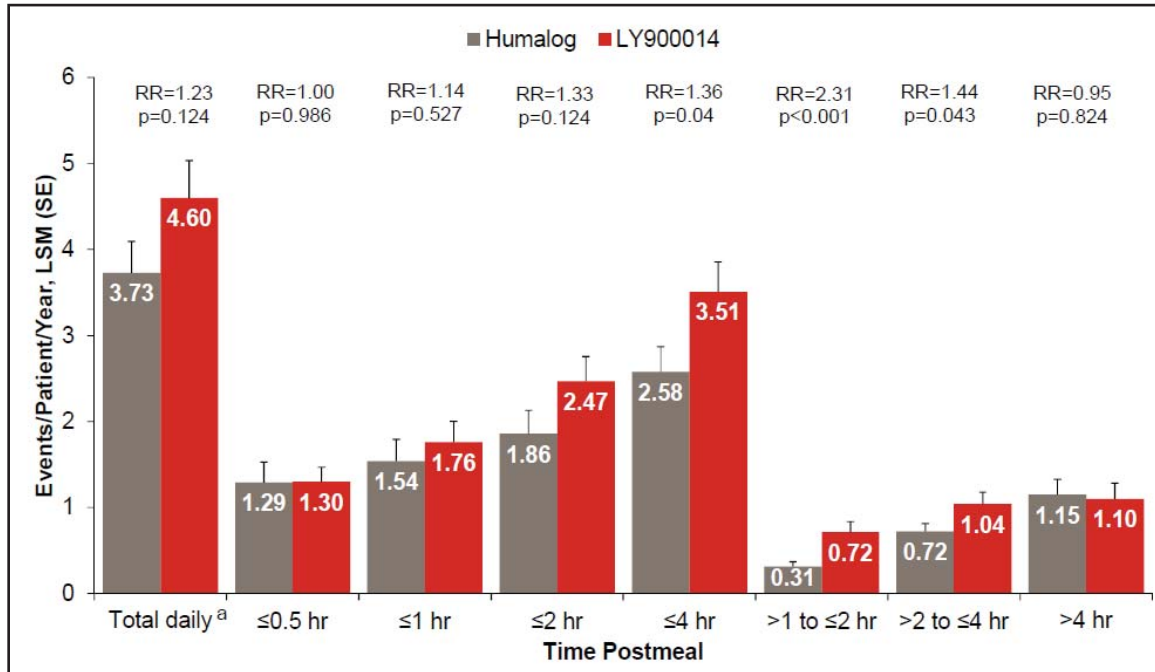
- No statistically significant treatment difference was noted at ≤ 4 , >2 to ≤ 4 , and >4 hours postmeal time intervals in the incidence of hypoglycemia with BG<54 mg/dL.
- A statistically significantly higher incidence of symptomatic and asymptomatic postmeal hypoglycemia with BG<54 mg/dL in the LY900014 group than in the Humalog group was noted at time intervals up to 2 hours following administration (≤ 0.5 , ≤ 1 , ≤ 2 , and >1 to ≤ 2 hours postmeal) (data available in CSR ITRN Table 14.164.).

Figure 19 presents a summary and analysis of the rate of documented symptomatic and asymptomatic postmeal hypoglycemia with BG <54 mg/dL by various time intervals after the start of a meal.

Rate:

- No statistically significant treatment difference was noted in the rate of hypoglycemia at ≤ 0.5 , ≤ 1 , ≤ 2 , and >4 hours postmeal.
- A statistically significantly higher rate of hypoglycemia in the LY900014 group than in the Humalog group was noted at ≤ 4 , >1 to ≤ 2 , and >2 to ≤ 4 hours postmeal.

Figure 19: Rate of Documented Symptomatic and Asymptomatic Postmeal Hypoglycemia (BG <54 mg/dL) from Week 0 - 26 Prior to Discontinuation of Study Drug in Study ITRN



Abbreviations: BG = blood glucose; LSM = least squares mean; RR = relative rate; SE = standard error.

^a Rate of daily documented asymptomatic and symptomatic hypoglycemia.

Source: Summary of Clinical Safety Figure 2.7.4.6

Reviewer comment:

- Similar to the findings in T1D study, mealtime LY900014 administration in the T2D study was associated with a comparable incidence and rate of severe hypoglycemia as Humalog.
- For hypoglycemia with BG < 54 mg/dL, the rate of symptomatic hypoglycemia was noted to be higher in the LY900014 arm as a consequence of 5 subjects with multiple events of symptomatic hypoglycemia (one subject with 30 events). Reassuringly, the rate and incidence of hypoglycemia with BG < 54 mg/dL in other subcategories (all documented, non-nocturnal, nocturnal) did not differ significantly between treatment arms.
- The pattern of postmeal hypoglycemia is consistent with the faster time-action profile of LY900014. The time period of >1 to ≤ 2 hours postmeal appears to be the most susceptible for hypoglycemia with LY900014 administration, as this interval has both a statistically significantly higher rate and incidence of hypoglycemia for LY900014 compared to Humalog.
- The Applicant is proposing the label include dosing as follows: **Administer LYUMJEV at the start of a meal or within 20 minutes after starting a meal subcutaneously into the abdomen, upper arm, thigh, or buttocks.** Study ITRN did not investigate postmeal dosing of LY900014 in patients with T2D. As the T2D population is less insulin sensitive, any adverse safety findings would more likely be captured in trials with T1D patients. For that reason, the reassuring hypoglycemia profile of postmeal dosing of LY900014 (detailed below) in

patients with T1D, supports a favorable benefit-risk assessment for postmeal LY900014 dosing to the T2D population

- *Postmeal dosing of LY900014 was shown to be noninferior to treatment with Humalog in terms of change in HbA1c after 26 weeks of treatment.*
- *From a safety perspective, postmeal dosing with LY900014 was comparable to mealtime Humalog in terms of hypoglycemia with no difference in the rate or incidence of severe or clinically significant hypoglycemia with BG < 54 mg/dL.*
- *The timing of postmeal hypoglycemia for postmeal LY900014 dosing occurred at timepoint of >2 to ≤4-hour.*
- *If patients were to dose LY900014 closer to mealtime, then it would be expected that the results on glycemic control would be more similar to mealtime dosing, and no worse than dosing at 20 minutes postmeal.*
- *The timing of postprandial hypoglycemic events with LY+20 occurred at later timepoints than with mealtime LY900014; however, the rate and incidence of hypoglycemia was not significantly higher than with Humalog.*
- *Overall, patients with T2D are less at risk for hypoglycemia. This is confirmed by the fact that the rate of hypoglycemia in the T2D study was 2-3 fold lower overall than the T1D study.*
- *Therefore, given the finding of non-inferiority in the efficacy analysis of postmeal dosing of LY900014 in change in HbA1c compared to Humalog, with no increased risk of hypoglycemia in the safety analysis, I concur with the Applicant's proposed dosage and administration of LY900014 at the start of a meal or within 20 minutes after starting a meal.*

8.5.1.3. Study ITSI

Severe Hypoglycemia

Table 38 presents a summary and analysis of the rate and incidence of severe hypoglycemia during each 6-week treatment period by treatment. There were no statistically significant treatment differences in the rate or incidence of severe hypoglycemia for the 6-week treatment period. Each treatment arm had 1 patient with 1 hypoglycemic event.

Documented BG < 54 mg/dL

Hypoglycemia rate and incidence were summarized for Weeks 0 to 4, 0 to 6 and 4 to 6 for each treatment. Due to the crossover design of Study ITSI, only Weeks 4 to 6 of each treatment period were used for treatment comparisons of hypoglycemia. **Table 39** presents a summary of the rate and incidence for each subcategory of documented clinically significant hypoglycemia (BG <54 mg/dL) for the safety population in Study ITSI during Weeks 4 to 6 of each 6-week treatment period. Although numerically higher for LY900014, there were no statistically significant treatment differences in the rate or incidence of all documented, documented symptomatic, nocturnal, or non-nocturnal hypoglycemia with BG <54 mg/dL.

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Postprandial hypoglycemia

There were no statistically significant differences in the incidence or rate of documented postmeal hypoglycemia < 54 mg/dL during Weeks 4 to 6 of each treatment period (data available in CSR ITSI Table ITSI.11.19.).

Table 38: Severe Hypoglycemia Rate and Incidence from First Dose to Last Dose of IP in Each 6-Week Randomized Treatment Period Study ITSI Safety Population

Treatment	N	Rate				Incidence		
		Mean (SD)	Median	Aggregate Rate/ 100 Years	p-value ^a	n (%)	Episodes	p-value ^b
Humalog	48	17.70 (122.60)	0.00	18.05	1.00	1 (2.1)	1	1.00
LY900014	49	16.94 (118.59)	0.00	17.61		1 (2.0)	1	

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 for comparison between LY900014 and Humalog was computed using Wilcoxon signed-rank test, based upon the event rates from individual patients who were dosed in both randomized treatment periods.

^b p-value for comparison between LY900014 and Humalog was computed using Prescott's exact test, based upon patients who were dosed in both randomized treatment periods.

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, times 36525 (for rate per 100 years).

Source: Summary of Clinical Safety Table 2.7.4.27.

Table 39: Hypoglycemia Rate (Adjusted for 1 Year) and Incidence for Documented Hypoglycemia BG < 54 mg/dL Weeks 4 to 6 in Each 6-Week Randomized Treatment Period Prior to Discontinuation of Study Drug Study ITSI Safety Population

Category/Subcategory of Treatment	Hypoglycemia N	Rate				Incidence		
		Mean (SD)	Median	Aggregate Rate/Year	p-value ^a	n (%)	Episodes	p-value ^b
BG <54 mg/dL								
Documented symptomatic hypoglycemia								
Humalog	47	2.19 (7.40)	0.00	2.23	0.064	4 (8.5)	4	0.201
LY900014	47	8.37 (21.31)	0.00	8.18		8 (17.0)	15	
All documented hypoglycemia								
Humalog	47	2.74 (8.17)	0.00	2.78	0.107	5 (10.6)	5	0.296
LY900014	47	8.37 (21.31)	0.00	8.18		8 (17.0)	15	
Non-nocturnal hypoglycemia								
Humalog	47	1.67 (6.63)	0.00	1.67	0.195	3 (6.4)	3	0.318 ^c
LY900014	47	5.32 (15.87)	0.00	5.45		6 (12.8)	10	
Nocturnal hypoglycemia								
Humalog	47	1.07 (5.15)	0.00	1.11	0.250	2 (4.3)	2	0.580
LY900014	47	3.05 (12.43)	0.00	2.73		3 (6.4)	5	

Abbreviations: BG = blood glucose; N = number of patient in the population with baseline and post-baseline value at the specified visit; n = number of patients

with hypoglycemia; SD = standard deviation.

a p-values for comparisons between LY900014 and Humalog were computed using Wilcoxon signed-rank test.

b Generalized linear mixed model with options of the binomial distribution and logit link function for post-baseline comparisons between treatment and control groups: Incidence = Period + Sequence + Treatment. Variance-Covariance = compound symmetry without heterogeneous variances.

c p-values for comparisons between LY900014 and Humalog were computed using Prescott's exact test.

Source: Summary of Clinical Safety Modified from Table 2.7.4.29.

Reviewer comment: While not statistically significant, the rate and incidence of clinically significant hypoglycemia in all subcategories were noted to be higher for LY900014 administered via CSII. Studies of larger size and longer duration are needed to determine if there is an increased risk of hypoglycemia posed by use of LY900014 in insulin pump devices.

8.5.2. Injection and Infusion Site Reactions

Injection or infusion site reactions are one of the frequently reported adverse drug reactions with insulin products. A customized MedDRA search of spontaneously reported AEs was used to identify potential injection site reaction AEs. An eCRF was also used to collect information on the presence and severity of injection site erythema, induration, pain, pruritus, and edema for injection site reaction AEs during the study.

MDI

A summary and analysis of all potential injection site reaction TEAEs reported during from randomization to safety follow-up in MDI studies is presented in **Table 40**.

There were statistically significantly more patients in the All LY group compared with the Humalog group with at least 1 potential treatment-emergent injection site reaction AE (All LY, 32 [2.9%]; Humalog, 4 [0.5%]; $p < 0.001$). The most frequently reported events were also reported at a significantly higher incidence in the All LY group and included *injection site pain* (All LY, 13 [1.2%], 18 events; Humalog, 0; $p = 0.002$) and *injection site reaction* (All LY, 12 [1.1%], 20 events; Humalog, 1 [0.1%], 1 event; $p = 0.026$).

None of the injection site TEAEs in the MDI studies were reported as SAEs. All events were mild (87.5%) or moderate (12.5%) in severity, and most events were reported as resolved or resolving during the study. One patient (All LY) discontinued study treatment due to a TEAE of *injection site oedema*.

Table 40: Potential Treatment-Emergent Injection Site Reactions Using MedDRA Search Terms from Randomization to Safety Follow-up Safety Population Studies ITRM and ITRN

Preferred Term	Humalog (N=779)			All LY (N=1116)			Total (N=1895)			OR* ^a	Heterogeneity	
	Number of TEAE	n	(%)	Number of TEAE	n	(%)	Number of TEAE	n	(%)		P-value* ^b	P-value* ^c
Subjects with ≥ 1 TEAE	4		(0.5)	32		(2.9)	36		(1.9)	5.15	0.118	<.001
Injection site bruising	0	0	(0.0)	2	2	(0.2)	2	2	(0.1)	NC	NC	0.287
Injection site erythema	0	0	(0.0)	3	3	(0.3)	3	3	(0.2)	NC	NC	0.111
Injection site haemorrhage	0	0	(0.0)	1	1	(0.1)	1	1	(0.1)	NC	NC	0.452
Injection site induration	0	0	(0.0)	2	2	(0.2)	2	2	(0.1)	NC	NC	0.214
Injection site oedema	0	0	(0.0)	1	1	(0.1)	1	1	(0.1)	NC	NC	0.317
Injection site pain	0	0	(0.0)	18	13	(1.2)	18	13	(0.7)	NC	NC	0.002
Injection site rash	0	0	(0.0)	1	1	(0.1)	1	1	(0.1)	NC	NC	0.452
Injection site reaction	1	1	(0.1)	20	12	(1.1)	21	13	(0.7)	7.10	0.694	0.026
Lipodystrophy acquired	1	1	(0.1)	0	0	(0.0)	1	1	(0.1)	0.00	NC	0.184
Lipohypertrophy	3	3	(0.4)	2	2	(0.2)	5	5	(0.3)	0.38	NC	0.267

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 analysis population; n = number of subjects with events meeting specified criteria; TEAE = Treatment-Emergent Adverse Event; NC = Not Calculable.

*^a $\hat{a}$ Mantel-Haenszel Odds Ratio stratified by study. All LY is numerator

*^b $\hat{a}$ Heterogeneity of odds ratios across studies was assessed using the Breslow Day test

*^c $\hat{a}$ 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 2.7.4.34

CSII

The incidence of TEAEs site reactions related to insulin administration was higher with CSII administration for both LY900014 and Humalog compared to MDI therapy. A summary and analysis of these events reported during each 6-week treatment period is presented in **Table 41**.

The incidence of potential treatment-emergent infusion site reactions was again statistically significantly higher for LY900014 compared with Humalog (LY900014, 19 patients [38.8%]; Humalog, 6 patients [12.5%]; $p = 0.006$). The most frequently reported events were *infusion site pain* (LY900014, 9 patients [18.4%]; Humalog, 2 patients [4.2%]) and *infusion site reaction* (LY900014, 9 patients [18.4%]; Humalog, 4 patients [8.3%]).

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All events were mild (98.2%) or moderate (1.8%) in severity. All treatment-emergent infusion site reactions resolved during the study with no change to dosing of IP. There were also no discontinuations due to infusion site reactions.

Table 41: Potential Treatment-Emergent Infusion Site Reactions Using MedDRA Search Terms from Randomization to Week 6 of Each Randomized Treatment Period Safety Population I8B-MC-ITSI

Events	Humalog	LY900014	p-value ^a
	(N=48) n (%)	(N=49) n (%)	
Patients with ≥ 1 TEAE	6 (12.5)	19 (38.8)	0.006
Infusion site pain	2 (4.2)	9 (18.4)	0.095
Infusion site reaction	4 (8.3)	9 (18.4)	0.415
Infusion site erythema	0	2 (4.1)	0.490
Infusion site pruritus	0	1 (2.0)	1.000

Abbreviations: N = number of subjects in the analysis population; n = number of subjects with at least one event meeting the specified criteria; TEAE = treatment-emergent adverse event.

a p-values for comparisons between LY900014 and Humalog were computed using Prescott's Exact test.

Source: Summary of Clinical Safety Table 2.7.4.35

Reviewer comment: *The higher incidence of injection site reaction events with LY900014 in comparison to Humalog is likely due to the excipients in the formulation, most likely treprostinil, resulting in localized erythema and discomfort. Not surprisingly, administration by continuous infusion resulted in a higher incidence of localized infusion site related TEAEs in comparison to MDI administration, with rates over 10-fold higher with LY900014 and 25-fold higher with Humalog with CSII than MDI. Despite this imbalance, there was only one study treatment discontinuation related to this TEAE in the Phase 3 studies. The AEs of injection site reactions are not a significant safety concern and are unlikely to limit clinical use; nevertheless, this information should be presented in the label, and the Applicant has appropriately provided this data in the Section 6.1.*

8.5.3. Hypersensitivity

In order to identify potential hypersensitivity reactions from the spontaneously reported AEs, the following standardized MedDRA queries (SMQs) were used: anaphylactic reaction, angioedema, and hypersensitivity. The results of this query revealed that similar proportions of patients in the All LY group and Humalog group reported events captured using the broad and narrow terms from the combined SMQs, with no statistically significant treatment differences (Humalog 39 [5.0%]; All LY 71 [6.4%]). The Applicant also presented the data based on the likelihood the TEAE was related to the study drug. This analysis also revealed similar

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proportions in each treatment arm (Humalog 2 [0.3%]; All LY 2 [0.2%]) (data available in Summary of Clinical Safety Appendix Table APP2.7.4.12 and Table APP2.7.4.13).

Reviewer comment: *Many of the events identified by the SMQs do not represent a clinically significant severe hypersensitivity event, but rather a more benign event that may not be drug related. For example, the majority of events identified as “anaphylactic reaction” were cough and asthma, while and seasonal allergy and eczema made up the vast majority of “hypersensitivity”. Overall, the various PTs and proportions reported were similar between LY900014 and Humalog and do not suggest a differing risk of hypersensitivity.*

8.6. Safety Analyses by Demographic Subgroups

The Applicant performed subgroup analyses on all available data, without regard to treatment status, and analyses with data while patients were on study drug. For the intrinsic factors of gender, age (<65 vs ≥65), BMI (<25 vs ≥25 kg/m²), ethnicity, race, and estimated glomerular filtration rate (eGFR), no clinically relevant treatment-by-subgroup interactions were observed (data available in Clinical Summary Safety Appendix).

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

Malignant and unspecified tumor events were identified, using the malignant tumors SMQ, and compared between treatment groups, and are summarized in **Table 42**. The number and percentage of patients with at least 1 potential treatment-emergent malignant neoplasm event was similar between the treatment groups (All LY 4 [0.4%]; Humalog 2 [0.3%]). Events reported were: *clear cell renal carcinoma, colon cancer, intraductal proliferative breast lesion, squamous cell carcinoma, and squamous cell carcinoma of skin*. Only *squamous cell carcinoma* (All LY, 2) was reported by more than 1 patient.

Reviewer comment: *There is no suggestion of any safety signal related to cancer with the insulin treatment. However, the studies in this clinical development program are too short in duration (12 months or shorter) to adequately evaluate carcinogenicity potential with a product.*

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Table 42: Potential Treatment Emergent Malignant Neoplasm Event Using MedDRA Search Terms from Randomization to Safety Follow-up Safety Population ITRM and ITRN

SNQ or sub-SMQ Classification*d Preferred Term	n	Humalog (N=779) (%)	n	All LY (N=1116) (%)	n	Total (N=1895) (%)	OR*a	Heterogeneity P-value*b	P-value*c
Subjects with >=1 TEAE - Malignant Neoplasm Event	2	(0.3)	4	(0.4)	6	(0.3)	1.59	0.151	0.624
Broad	2	(0.3)	4	(0.4)	6	(0.3)	1.59	0.151	0.624
Narrow	2	(0.3)	4	(0.4)	6	(0.3)	1.59	0.151	0.624
Malignant Tumours (SMQ)									
Broad	2	(0.3)	4	(0.4)	6	(0.3)	1.59	0.151	0.624
Clear Cell Renal Cell Carcinoma	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.318
Colon Cancer	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Intraductal Proliferative Breast Lesion	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Squamous Cell Carcinoma Of Skin	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.318
Squamous Cell Carcinoma	0	(0.0)	2	(0.2)	2	(0.1)	NC	NC	0.214
Narrow	2	(0.3)	4	(0.4)	6	(0.3)	1.59	0.151	0.624
Clear Cell Renal Cell Carcinoma	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.318
Colon Cancer	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Intraductal Proliferative Breast Lesion	0	(0.0)	1	(0.1)	1	(0.1)	NC	NC	0.452
Squamous Cell Carcinoma Of Skin	1	(0.1)	0	(0.0)	1	(0.1)	0.00	NC	0.318
Squamous Cell Carcinoma	0	(0.0)	2	(0.2)	2	(0.1)	NC	NC	0.214

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 analysis population; n = number of subjects with events meeting specified criteria; TEAE = Treatment-Emergent Adverse Event; NC = Not Calculable.

*a – Mantel-Haenszel Odds Ratio stratified by study. All LY is numerator

*b – Heterogeneity of odds ratios across studies was assessed using the Breslow Day test

*c – p-values are from Cochran-Mantel-Haenszel (CMH) test of general association stratified by study.

*d - MedDRA SMQ preferred term classification. Broad classification includes preferred terms within the narrow classification.

Source: ISS Table ISS.4.24

8.8.2. Human Reproduction and Pregnancy

The safety of LY900014 has not been studied during pregnancy and lactation in clinical studies. In the clinical development program for LY900014, women of childbearing potential were required to use contraceptive methods, and pregnancy or intent to become pregnant were exclusion and withdrawal criteria.

A total of 7 patients, all in Study ITRM (All LY, 5; Humalog, 2), discontinued study treatment due to pregnancy in the Phase 3 trials. All pregnancies occurred within the first 6 weeks of randomization, after the lead-in period, and all patients discontinued study medication.

Review of the case narratives revealed that of the 2 patients from the Humalog treatment arm, one had an uncomplicated pregnancy with delivery of a healthy infant while the other patient suffered pre-eclampsia necessitating a Cesarean-section at 34 weeks which resulted in a good outcome for both fetus and mother. None of the five patients receiving LY900014 had viable pregnancies. One case involved a 32-year-old African American woman G1P1 who suffered a spontaneous abortion at approximately 6 weeks. The second patient was diagnosed with an ectopic pregnancy and another patient was discovered to have an empty sac on fetal ultrasound. The final two cases involved patients with advanced maternal age: one age 42 years

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with concomitant history of tobacco and alcohol use, the other age 44 years with a prior history of multiple spontaneous abortions.

Reviewer comment: *While its concerning that none of the five patients with LY900014 exposure had term pregnancies, causality of these events to the study drug is not clearly linked in these cases. The cases involving empty sac and ectopic pregnancy were unlikely related to use of the drug, and two additional cases had confounding factors increasing risk of complications in pregnancy including maternal and pre-existing T1D.*

8.8.3. Pediatrics and Assessment of Effects on Growth

There are no completed pediatric studies for review with the use of LY900014. The Applicant reached agreement with FDA on December 4, 2017 on the initial Pediatric Study Plan (iPSP) for LY900014 under IND 127210. The Applicant is requesting partial waver for clinical studies in patients under 1 year of age with T1D and under 10 years of age with T2D. A pediatric deferral is also requested for T1D for completion of the Phase 3 safety and efficacy study (ITSB) since adult studies are completed and under BLA review. Study ITSB was initiated April 7, 2019 following review of safety and efficacy data from ITRM and review of data from pediatric PK/PD study (ITSA). No clinical studies are proposed in pediatric patients with T2D. The Applicant intends (b) (4)

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

Neither LY900014, nor Humalog, 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.

8.9. Safety in the Postmarket Setting

As LY900014 is not yet marketed, no postmarketing experience exists for this product.

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable.

8.9.3. Additional Safety Issues from Other Disciplines

See **Section 4.2** for concerns regarding compatibility identified in CMC review.

8.10. Integrated Assessment of Safety

The safety findings for LY900014 during the Phase 3 trials did not reveal any new safety signals or concerns. The pooled MDI safety data showed no difference in the incidence of SAEs between Humalog (12.8%) and LY900014 (10.1%), with hypoglycemia being the most common SAE in the T1D population, and infections (pneumonia and cellulitis) the most common SAE in patients with T2D.

The known risks commonly associated with use of insulin products include hypoglycemia, hypersensitivity, and injection site reactions. No difference in the incidence of potential hypersensitivity AEs was noted in the safety population. With the faster-time action profile and novel excipients in LY900014, the AEs of hypoglycemia and injection site reactions were examined more carefully.

The hypoglycemia safety profile for LY900014 was found to be very similar to Humalog. In patients with T1D, the incidence of severe hypoglycemia was low and did not differ between subjects receiving Humalog or LY900014, dosed either at mealtime or 20 minutes after meals [LY900014 (5.5%); Humalog (5.7%); LY+20 (4.6%)]. The rate and incidence of postprandial hypoglycemia with mealtime LY900014 was very similar to Humalog and occurred at earlier timepoints (>1 to ≤ 2 hours). Congruent with the timing of administration, with LY+20, postprandial hypoglycemia occurred more often at a slightly later timepoint (>2 to ≤ 4 hours). In the T2D population, the incidence of severe hypoglycemia was low and did not differ between Humalog (1.78%) and LY900014 (0.89%). The rate and incidence of postprandial hypoglycemia were both significantly higher with LY900014 than Humalog at timepoints (>1 to ≤2 hours), similar to what was seen with mealtime LY900014 in the T1D population. Overall, treatment with mealtime LY900014 and LY+20 was not associated with an unacceptable hypoglycemia risk.

The incidence of TEAEs related to injection site reactions were statistically significant higher in patients receiving LY900014. In the pooled MDI safety data, the incidence of injection site reaction AE for LY900014 (2.9%) was significantly higher than Humalog (0.5%), with the most frequently reported events of *injection site pain* and *injection site reaction*. All events were mild (87.5%) or moderate (12.5%) in severity, and only one patient, on LY900014, discontinued study treatment due to a TEAE of *injection site oedema*. Patients on CSII therapy overall had higher incidence of TEAEs related to infusion site reactions than MDI treatment, which also was significantly higher for LY900014 (38.8%) treatment group compared with Humalog (12.5%). The most frequently reported events were *infusion site pain* and *infusion site reaction*. The vast majority of these events were graded as mild in severity (98%) and no discontinuations or changes in insulin dosing occurred with these events. Overall, the AEs associated with injection site reaction do not pose a safety concern.

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In summary, the safety data from the Phase 3 studies suggest that LY900014 is safe, posing no significantly increased risks to patients than currently marketed insulin products. The hypoglycemia profile of LY900014 was similar to Humalog. No significant differences were noted in the incidence of severe or clinically significant hypoglycemia. The timing of postprandial hypoglycemia events with LY900014 was indicative of its faster PD profile. The incidence of reported injection site reaction related AEs was significantly higher with LY900014 compared to Humalog, most likely due to the vasodilatory effects of the excipient, treprostinil. However, the majority of these injection site related AEs were transient, mild to moderate in severity, and did not interrupt or modify dosing during clinical treatment.

9. Advisory Committee Meeting and Other External Consultations

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

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling has been discussed throughout this review and labeling negotiations with the Applicant are currently ongoing. The following is a summary of the items for which I recommend changes to the label as proposed by the Applicant.

- I recommend in Section 2 for IV administration include a statement that dilutions below 1 U/mL are not recommended, due to the uncertainty of insulin delivery at lower dilutions.
- I recommend exclusion of [REDACTED] (b) (4)
- I recommend exclusion of the [REDACTED] (b) (4)
- I recommend the exclusion of [REDACTED] (b) (4)

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- (b) (4)
- (b) (4)
- I recommend exclusion of

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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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): ITRM, ITRN, ITS1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>663</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
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 influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)

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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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Supplemental Tables and Figures

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Table 43 Study Schedule ITRM, ITRN

Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period								Maintenance Period	Long Term Maintenance Period (Double Blind Arms Only)				Safety Follow-Up	ED		
		2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15		16	17	18	19			20	21
eCRF Visit Number	1																						801	ED ^b
Visit Window (± days)		3	3	3	3	3	3	4	3	3	7	7	7	7	7	7	7	7	7	7	7	7	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-9	-8	-7	-6	-4	-2	-1	0	1	2	4	6	8	10	12	18	22	26	32	39	46	52	56 (30) ^c	
Informed consent signed	X																							
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient eligibility review	X																							
Randomization ^d								X																
Telephone call for visit reminder or informing patient of completion in the study																								X
Clinical Assessments																								
Patient demographics	X																							
Medical history and preexisting conditions	X																							

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Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period								Maintenance Period			Long Term Maintenance Period (Double Blind Arms Only)				Safety Follow-Up	ED	
		2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15	16	17	18	19	20	21	22			
eCRF Visit Number	1																						801	ED ^b	
Visit Window (± days)		3	3	3	3	3	3	4	3	3	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-9	-8	-7	-6	-4	-2	-1	0	1	2	4	6	8	10	12	18	22	26	32	39	46	52	56 (30) ^c		
Physical exam/height	X																								
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs and product complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight ^e	X	X			X		X	X		X	X		X		X	X	X	X	X	X	X	X	X	X	
Vital signs: blood pressure/ pulse rate ^f	X	X			X		X	X		X	X		X		X	X	X	X	X	X	X	X	X	X	
ECG ^g (12-lead; local)	X																								
Diabetes and nutrition counseling ^h		X																							
Transfer to Humalog ⁱ		X																							
Transfer to allowed study basal insulin regimen ^j		X																							

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Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period								Maintenance Period	Long Term Maintenance Period (Double Blind Arms Only)				Safety Follow-Up	ED			
		2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15		16	17	18	19			20	21	22
eCRF Visit Number	1																						801	ED ^b	
Visit Window (± days)		3	3	3	3	3	3	4	3	3	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-9	-8	-7	-6	-4	-2	-1	0	1	2	4	6	8	10	12	18	22	26	32	39	46	52	56 (30) ^c		
Basal and prandial insulin dose assessment ^k		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Titrate basal insulin ^k		X	X	X	X	X	X																		
Titrate prandial insulin ^l								X	X	X	X	X	X	X											
Ancillary Supplies/Diaries/IP																									
Dispense blood glucose meter and ancillary supplies and complete training ^{m,n}		X						X		X	X		X		X	X	X	X	X	X	X	X	X		
Dispense eCOA and complete training ⁿ		X																							

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Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period										Maintenance Period			Long Term Maintenance Period (Double Blind Arms Only)				Safety Follow-Up	ED
		2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15	16	17	18	19	20	21	22	801	ED ^b		
eCRF Visit Number	1	2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15	16	17	18	19	20	21	22	801	ED ^b		
Visit Window (± days)		3	3	3	3	3	3	4	3	3	7	7	7	7	7	7	7	7	7	7	7	7	7			
Time on Study Relative to First Active Treatment Dose (weeks)	-9	-8	-7	-6	-4	-2	-1	0	1	2	4	6	8	10	12	18	22	26	32	39	46	52	56 (30) ^c			
Train on collecting 4- and 10-point SMBG profiles ⁿ		X																								
Review 4-point SMBG profiles			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Remind patient of 10-point SMBG requirements ^o						X	X			X		X		X			X		X		X					
Review 10-point SMBG Profiles								X			X		X		X			X		X		X		XP		
Review/discuss hypo data			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense IP		X			X			X			X		X		X	X	X	X	X	X	X					
Return of eCOA devices																							X	X		
Patient returns used and unused study drug supplies					X			X			X		X		X	X	X	X	X	X	X	X		X		

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Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period										Maintenance Period			Long Term Maintenance Period (Double Blind Arms Only)				Safety Follow-Up	ED
		2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15	16	17	18	19	20	21	22				
eCRF Visit Number	1	2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15	16	17	18	19	20	21	22	801	ED ^b		
Visit Window (± days)		3	3	3	3	3	3	4	3	3	7	7	7	7	7	7	7	7	7	7	7	7	7			
Time on Study Relative to First Active Treatment Dose (weeks)	-9	-8	-7	-6	-4	-2	-1	0	1	2	4	6	8	10	12	18	22	26	32	39	46	52	56 (30) ^c			
Drug accountability					X			X			X		X		X	X	X	X	X	X	X	X		X		
Laboratory Assessments																										
Patient fasts prior to visit		X						X										X					X		X	
MMTT ^q								X										X								
Urinalysis panel	X																									
Pregnancy test ^r	X							X																		
Follicle-stimulating hormone test ^s	X																									
Chemistry panel	X							X										X					X		X	
Fasting serum glucose		X																								
Hematology	X							X										X					X		X	
1,5-AG								X			X				X			X			X		X		X	
HbA1c	X						X	X			X		X		X			X			X		X	X	X	
Lipid profile								X										X					X		X	
Pharmacogenetic sample ^t								X																		

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Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period								Maintenance Period	Long Term Maintenance Period (Double Blind Arms Only)				Safety Follow-Up	ED		
		2	3 ^a	4 ^a	5	6 ^a	7	8	9 ^a	10	11	12 ^a	13	14 ^a	15		16	17	18	19			20	21
eCRF Visit Number	1																						801	ED ^b
Visit Window (± days)		3	3	3	3	3	3	4	3	3	7	7	7	7	7	7	7	7	7	7	7	7	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-9	-8	-7	-6	-4	-2	-1	0	1	2	4	6	8	10	12	18	22	26	32	39	46	52	56 (30) ^c	
Nonpharmacogenetic biomarker storage samples								X										X						X
Anti-insulin lispro antibodies		X						X		X	X				X			X				X	X ^u	X
Health Outcomes Questionnaires^v																								
ITSQ		X						X									X					X		X
EQ-5D-5L		X						X									X					X		X
WPAI-GH		X						X									X					X		X

Abbreviations: 1,5-AG = 1,5-anhydroglucitol; AEs = adverse events; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment, eCRF = electronic case report form; ED = early discontinuation; EQ-5D-5L = European Quality of Life – 5 Dimensions, 5 Levels; hypo = hypoglycemia; HbA1c = hemoglobin A1c; IP = investigational product; ITSQ = Insulin Treatment Satisfaction Questionnaire; IWRS = interactive web response system; MMTT = mixed-meal tolerance test; SMBG = self-monitored blood glucose; WPAI-GH = Work Productivity and Activity Impairment Questionnaire General Health.

Schedule of Activities

- d Telephone visits are indicated by shaded columns. Activities included:
- Record visit in the IWRS.
 - Collect AEs and concomitant medications.
 - Review blood glucose readings and study drug doses.
 - Adjust prandial insulin or basal insulin doses, as needed.
 - Review hypoglycemic events.
 - Provide reminders regarding scheduled visits, fasting, and SMBG profiles, as applicable.
- e Patients who had been randomized were asked to return for the ED visit in a fasting state, unless patient was already fasting and at the site when the decision to discontinue was made. Patients who discontinued during the lead-in period prior to randomization who were not already at the site, were asked to return for the ED in a nonfasting state and all activities should have been completed, except for laboratory tests and questionnaires (ITSQ, EQ-5D-5L, and WPAI-GH).
- f Patients randomized to the open-label treatment group completed the study at Week 30, unless patient continued into the insulin antibody assessment period. It was recommended that the first insulin lispro antibody follow-up visit (Visit 802) was scheduled for all study patients, regardless of treatment-emergent antibody status. Visit 802 should have occurred approximately 13 weeks after Visit 801.
- g Randomization should have occurred after all Visit 8 procedures including MMTT. If MMTT was rescheduled post-Visit 8, randomization should not have occurred until baseline MMTT was completed. The patient administered their first dose of study insulin with the first meal after the MMTT was completed and randomization had occurred.
- h Patients should have been advised to remove their shoes and empty their pockets before the body weight was obtained.
- i Vital sign measurements must have been taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. These measurements should have been determined after patients had been seated quietly for at least 5 minutes in a chair with feet on the floor. The arm used for blood pressure measurement should have been supported at heart level.
- j Patients must have been supine for approximately 5 to 10 minutes before ECG collection and remained supine, but awake, during ECG collection.
- k Initial training at Visit 2 included diabetes education and nutrition counseling. Appropriate site personnel administered training and education using locally approved diabetes education/training materials or other materials provided by the Sponsor. Patients may have been provided abbreviated training and education at visits following Visit 2, as appropriate.
- l Only applied to patients on insulin glulisine or insulin aspart.
- m Patients were transferred to a study basal insulin regimen at Visit 2. Investigators determined the appropriate basal insulin regimen for each patient. It was expected that most of the basal insulin dose adjustments should have occurred during the lead-in period. However, basal insulin titration may have continued during the intensive titration period for patients who needed more intensification to achieve glycemic targets. Basal insulin dose adjustments during the maintenance period should have been made for safety reasons, such as hypoglycemia and unacceptable hyperglycemia.
- n Assessments of the basal insulin dose should have been made, at minimum, weekly during the lead-in period, including Weeks -5 and -3. Assessment of the prandial insulin dose should have been made, at minimum, weekly during the initial 12 weeks after randomization, including Weeks 3, 5, 7, 9, and 11.

Clinical Review

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Lyumjev, insulin lispro

- o During the lead-in period, prandial doses, correction factors, and insulin-to-carbohydrate ratios should have been evaluated and adjustments should have been made for safety reasons, such as hypoglycemia and unacceptable hyperglycemia. During the intensive titration period, prandial insulin dose should have been adjusted in order to meet the target SMBG levels. Further adjustments during the maintenance period should have been made for safety reasons, such as hypoglycemia and unacceptable hyperglycemia.
- p Glucose monitoring supplies were dispensed at other visits, as needed.
- q Training may have been repeated at other visits, as needed.
- o Patients in all 3 study arms should have been instructed to perform three 10-point SMBG profiles during a 2-week period. The 10-point profile was completed over a 1-day period, preferably on 3 nonconsecutive days (weekdays and weekends). Ten-point SMBG profiles should not have been performed on the day of MMTT.
- P Review of 10-point SMBG profiles at the ED visit took place only for patients randomized into the study.
- q MMTT could occur 0 to 4 days prior to the visit, and patient must have been fasting prior to start of the MMTT.
- r Serum pregnancy test must have been performed in women of childbearing potential at Visit 1, followed by a urine pregnancy test within 24 hours prior to IP exposure at randomization (Visit 8) and at other times at the investigator's discretion. When required per local regulations and/or institutional guidelines, local pregnancy testing occurred at mandatory times during the study treatment period.
- s Follicle-stimulating hormone test must have been performed at Visit 1 for a postmenopausal woman who was between 50 and 54 years of age (inclusive) with an intact uterus, not on hormone therapy, and who had had at least 6 months of spontaneous amenorrhea.
- t Pharmacogenetic sample could be collected at any other visit if not collected at Visit 8
- u Patients with treatment-emergent insulin lispro antibodies measured at Visit 801 who had not returned to prespecified baseline range (Visit 2), were asked to undergo additional antibody monitoring. This follow-up assessment also applied to any patient who discontinued study insulin treatment prior to the end of the planned treatment period who had a treatment-emergent antibody response that had not returned to baseline range by Visit 801. It was recommended that the first insulin lispro antibody follow-up visit (Visit 802) was scheduled for all study patients, regardless of treatment-emergent antibody status.
- v Health outcomes questionnaires were administered at the study sites, based on the availability of appropriate translations. The questionnaires should have been administered prior to other study procedures, except at Visit 8 and Visit 18 when questionnaires may have been administered following the start of the MMTT.

Source: Table ITRM9.6 ITRM CSR week 52

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