30 January 2020
EMA/86760/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Liumjev

International non-proprietary name: insulin lispro

Procedure No. EMEA/H/C/005037/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibodies (anti-insulin lispro antibodies)
ADME	Absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of specific interest
1,5-AG	1,5-anhydroglucitol
AIT	Active insulin time
All LY	LY900014 administered 0 to 2 minutes prior to the start of the meal or at 20 minutes after the start of the meal
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Assessment report
AST	Aspartate transaminase
AUC	Area under the (concentration-time) curve
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
CGM	Continuous glucose monitoring
CI	Confidence interval
CL	Clearance
C_{max}	Maximal concentration
CR	Carbohydrate ratio
CRU	Clinical research unit
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical study report
CSS	Clinical safety summary
dL	Decilitre
DM	Diabetes mellitus
DOA	Duration of action
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life – 5 Dimensions, 5 Level questionnaire
ERB	Ethical Review Board
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGM	Flash glucose monitoring
FPG	Fasting Plasma Glucose
FSE	First subject enrolled
GCP	Good Clinical Practice

GD	Glucodynamic(s)
GIR	Body weight standardized glucose infusion rate
GIR_{max}	Maximum smoothed body weight standardized GIR
GIR-t_{max}	time to GIR_{max}
GLS	Geometric least square
GM	Geometric mean
GMR	Geometric mean ratio
HbA1c	Glycated haemoglobin
HF	Human factor
HO	Health outcome
Hr	Hour
ICH	International Conference on Harmonisation
ID	Identification
IP	Investigational product
IR-A	Insulin receptor, subtype A
IRB	Institutional Review Board
IR-B	Insulin receptor, subtype B
ISF	Insulin sensitivity factor
ITSQ	Insulin Treatment Satisfaction Questionnaire
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
LADA	Late autoimmune diabetes in adults
LOCF	Last observation carried forward
LOQ	Limit of quantitation
LSM	Least squares means
MA	Marketing Authorisation
MAA	Marketing authorisation application
MAH	Marketing Authorisation Holder
MAR	Missing at Random
MDI	Multiple daily injections
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Millilitre
MMRM	Mixed-effects model for repeated measures
MMTT	Mixed meal tolerance test
MNOR	Missing non at random
MoA	Mechanism of action
MODY	Maturity-onset diabetes in the young
Nab	Neutralizing antibody
ND	Not done
NDRI	Norepinephrine–dopamine reuptake inhibitor
NEC	Not Elsewhere Classified
NI	Non-inferiority
NIMP	Non-inferiority margin
NIMP	Noninvestigational medicinal product

OAM	Oral antihyperglycaemic medication
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PL	Product Leaflet
PP	Per-Protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient reported outcome
PSUR	Periodic Safety Update Report
PSUSA	PSUR Assessment
rDNA	Recombinant deoxyribonucleic acid
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SGLT-2	Sodium glucose cotransporter 2
SmPC	Summary of Product Information
SMBG	Self-monitored blood glucose
SMQ	Standardized MedDRA Query
SOC	System organ class
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TEADA	Treatment-emergent anti-drug antibodies
Tmax	Time to maximal concentration
U	Unit (of insulin)
ULN	upper limit of normal
US	United States
VAS	Visual analogue scale
VPC	Visual predictive check
WPAI-GH	Work Productivity and Activity Impairment Questionnaire General Health

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 8 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Liumjev, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: Treatment of diabetes mellitus in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration

The assessment of the current application includes an assessment of the applicant's claim that Liumjev does not fall within the scope of Article of Article 82(1) of Reg 726/2004 due to significant differences in safety and efficacy related to difference in excipients between Liumjev and Humalog that shares the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form and for which the Applicant holds a marketing authorisation.

Scientific advice

The applicant received Scientific Advice on 23 June 2016 (EMEA/H/SA/3333/1/2016/III) and on 23 February 2017 (EMEA/H/SA/3491/1/2017/I) for the development programme in question. The Scientific Advice pertained to the following Quality, Non-clinical and Clinical aspects:

- Acceptability of treprostinil as an excipient in the context of the developed formulation
- Sufficiency of proposed physicochemical and biochemical tests to establish comparability after change of the drug substance manufacturing process without the need for non-clinical or clinical studies
- Adequacy not to conduct rodent carcinogenicity studies given the minimal systemic treprostinil exposure with the intended therapeutic use and the inherently low carcinogenic potential of treprostinil
- Acceptability not to conduct a juvenile animal toxicity study based on the minimal systemic treprostinil exposure expected and the absence of reproductive and developmental toxicity in nonclinical studies of marketed treprostinil containing medicinal products
- Acceptability not to conduct PK studies in subjects with renal or hepatic impairment, drug-drug-interaction or a thorough QT study based on the proposed clinical pharmacology plan characterising PK and PD differences between established and new insulin lispro formulations

- Agreement that clinical pharmacology studies assessing the PK of the treprostinil excipient in special populations or drug-drug interaction studies are not required
- Adequacy of the proposed Phase 3 study plans to support benefit/risk assessment in patients with Type 1 and Type 2 Diabetes Mellitus using either a multiple dose insulin (MDI) or insulin pump (CSII) with a focus on the proposed primary efficacy endpoint, comparator use, definition of the study population, duration of studies and timing of injections
- Adequacy of the planned number of patients to be exposed in Phase 3 trials for the duration specified to support benefit/risk assessment at the time of MA
- Acceptability of the proposed primary analysis methods and non-inferiority margin for the Phase 3 studies
- Adequacy of the proposed measures for type-I error control across analyses in the Phase 3 studies
- Acceptability of continuous glucose monitoring (time in range) as a clinical meaningful measure of glucose control
- Acceptability of the proposed immunogenicity assessment and loss of efficacy by deterioration of glycaemic control as surrogate for neutralising insulin antibodies
- Acceptability of global enrolment plans for the Phase 3 studies
- Adequacy of the planned paediatric development with a view to timing of studies and demonstration of PK comparability to adults for both planned dose strengths (100 U/ml and 200 U/ml)

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Bart Van der Schueren

The application was received by the EMA on	8 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 June 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 October 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 November 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	23 January 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Liumjev on	30 January 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Chronic hyperglycaemia defines diabetes, and glycaemic control is fundamental to diabetes management. Improvement in long-term glucose control has been demonstrated to reduce the incidence

and progression of complications in people with type 1 (T1DM) or type 2 diabetes mellitus (T2DM). Both fasting glycaemia and glycaemic excursions occurring after meals contribute to overall glycaemic burden, a major contributor to the microvascular and macrovascular complications of diabetes. According to the 2011 International Diabetes Federation (IDF) guideline for management of post-meal glucose in diabetes, hyperglycaemia after meals is associated with an increased risk of micro- and macrovascular complications and should be addressed as part of the diabetes treatment regimen.

2.1.2. Clinical presentation

Control of glycaemic excursions after meals contributes to lowering the glycosylated haemoglobin (HbA_{1c}) level. As HbA_{1c} decreases, the relative contribution of post-meal glucose control on HbA_{1c} levels increases. Thus, in order to achieve recommended HbA_{1c} targets (<7%), it is important to address post-meal hyperglycaemia in addition to fasting hyperglycaemia, and control of post-meal glucose levels has received recognition as a therapeutic target for optimising glycaemic control in people with diabetes.

2.1.3. Management

In healthy individuals, approximately 50% of the total daily insulin secretion is basal insulin secretion. The other half of daily insulin secretion occurs postprandially. Carbohydrates absorbed from a meal cause a postprandial glucose elevation that triggers an acute surge of insulin from pancreas. This "first phase" of insulin spike, corresponding to secretion of preformed insulin from storage granules within the β cell, promotes peripheral utilization of the prandial nutrient load, suppresses hepatic glucose production, and limits postprandial glucose elevation. First-phase insulin secretion begins within 2 minutes of nutrient ingestion and continues for 10 to 15 minutes. This is followed by the second phase of prandial insulin secretion, corresponding to *de novo* production of insulin, which is sustained until normoglycaemia is restored.

Rapid-acting insulin analogues, first of which was insulin lispro, were developed to enable efficient postprandial glucose control. Compared to regular human insulin, insulin lispro has a more rapid onset, higher peak and shorter duration of action, which better fits for controlling postprandial glucose excursions. The daily insulin regimen is adjusted individually for every patient. Prandial insulin boluses are titrated based on glucose monitoring and carbohydrate content of the meal to achieve glycaemic targets.

Even with rapid-acting insulin analogues, efficient control of postprandial glucose elevation requires preprandial administration of insulin, optimally 15 to 20 minutes before the start of a meal, so that the peak insulin concentration occurs concomitantly with postprandial glucose elevation. In many instances, appropriate timing is not feasible; e.g. if the patient cannot anticipate the time of meal or amount of ingested carbohydrates. In such cases, prandial insulin is injected during or after the meal instead of before meal. Hence, there is need for more rapid insulin formulations than current rapid-acting analogue insulins such as lispro (Humalog, Liprolog, Insulin lispro Sanofi), aspart (NovoRapid), or glulisine insulin (Apidra). There already is on the market one ultra-rapid mealtime insulin product, Fiasp-insulin: insulin aspart formulation in which the addition of nicotinamide (vitamin B3) results in a faster initial absorption of insulin.

Targeting postprandial glycaemia has long been identified an important target in T1D patients, for whom the multiple daily injection (MDI) regimen, or alternatively, continuous subcutaneous insulin infusion with external insulin pump, aims at mimicking physiological insulin secretion. Depending on the patient's lifestyle, including diet and exercise, insulin formulations with various glucodynamic action profiles are needed. If the patient consumes large amounts of fast carbohydrate at meal, quicker action profile is needed from the prandial insulin than for a patient who avoids carbohydrates and prefers protein, as time

is needed for metabolizing protein into glucose. Furthermore, actively exercising individuals may need a formulation that doesn't have a prolonged hypoglycaemic effect that would hinder exercising after several hours of administration.

Currently, postprandial control of glycaemia is regarded to be important for type 2 diabetic (T2D) patients as well, as postprandial glucose (PPG) is a key contributor to overall glycaemic control, and represents a primary target to improve HbA1c levels and, in turn, to reduce the micro- and macrovascular complications of diabetes (Ceriello, Monnier). The relative contributions of PPG and fasting plasma glucose (FPG) to hyperglycaemia vary according to HbA1c value, with PPG contributing more in well-controlled individuals and FPG in those with poor control (Madsbad). According to current treatment standards (American Diabetes Association; Davies et al) targeting postprandial glycaemia is most relevant for T2D patients whose individual HbA1c goals are not met despite reaching preprandial glucose goals. The current target for postprandial glucose peak for most non-pregnant diabetic patients is <10 mmol/L. It is to be noted that for T2D patients, other options on controlling postprandial hyperglycaemia are primary before starting insulin, such as SGLT2-inhibitors, GLP-1 receptor agonists or other increting-based therapies (Davies et al). Insulin treatment typically causes weight gain in T2D patients, especially if multiple daily injections are used. Therefore, MDI regimen is usually only started when glycaemia cannot be controlled with other treatment options. This often occurs when the patient has a long history of diabetes and already advanced deficiency in insulin secretion.

About the product

LY900014 is a new formulation of insulin lispro [rDNA origin], that is being developed by the Applicant as an ultra-rapid insulin, for the treatment of patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM). The LY900014 formulation utilizes 2 enabling excipients: treprostinil and citrate with independent mechanisms to accelerate the absorption of insulin lispro from the site of injection or infusion resulting in a faster insulin time-action profile and in earlier glucose lowering when compared to Humalog. Lilly is the marketing authorization holder (MAH) and innovator of Humalog for which the same insulin lispro drug substance is used. Humalog was approved in the EU in 1996. Currently this application is intended for use in adults; however, paediatric development is ongoing.

Insulin lispro is an analogue protein of human insulin, obtained by recombinant DNA technology, that has a reverse position of the amino acids at positions 28 (lysine) and 29 (proline) on insulin's B chain when compared to the natural sequence of the human insulin. This structural change renders lispro insulin less prone to self-association than human insulin. The relatively unstable lispro hexamers readily dissociate to monomer subunits (without the intermediate dimerization as human insulin); this explains why lispro insulin is absorbed more rapidly after subcutaneous injection than human regular insulin. Consequently, insulin lispro has a faster onset and shorter duration of glucose-lowering action than human regular insulin when administered subcutaneously.

Once insulin lispro in LY900014 is absorbed into the systemic circulation, it is expected that distribution, action, and metabolic clearance are the same as insulin lispro in Humalog.

The purpose of development of LY900014 has been to provide a faster glucose-lowering effect that mimics more closely the physiological carbohydrate absorption profile and mealtime insulin response than the currently available insulin lispro products with the global trade names Humalog and Liprolog (duplicate licence), without compromising the safety. On the EU market there is also Insulin lispro Sanofi, a biosimilar lispro insulin.

LY900014 will be made available as a solution for SC injection or continuous subcutaneous infusion (CSII). LY900014 will also be available for IV use, under medical supervision.

LY900014 will be made available in two dosage strengths: 100 units/mL and 200 units/mL.

Effects of LY900014 on blood glucose concentration was investigated in patients with T1D, patients with T2D, and in healthy subjects.

Type of Application and aspects on development

Two multiple daily injection (MDI) Phase 3 studies were conducted to establish the efficacy of LY900014 to improve glycaemic control: Study I8B-MC-ITRM (called ITRM in this AR) in patients with T1D, and Study I8B-MC-ITRN (called ITRN in this AR) in patients with T2D. A third Phase 3 study, Study I8B-MC-ITSI (ITSI), provides additional evidence of efficacy when administered via continuous subcutaneous insulin infusion (CSII).

A total of 421 healthy subjects and 342 patients with T1D or T2D were exposed to LY900014 in the 22 completed clinical pharmacology trials. Altogether 1944 patients with T1D or T2D received study drug (LY900014 or the active comparator Humalog) in the Phase 3 studies, of which 1165 received LY900014.

A paediatric patient PK/PD comparing Humalog versus LY900014 in children and adolescents (6 to <18 years) with T1D is ongoing. A Phase 3 trial is planned for 2019. The Applicant plans to submit an indication for children once both trials are complete.

In the Scientific Advices (SA) on nonclinical aspects, it was agreed that treprostinil is an excipient and rodent 2year carcinogenicity studies and separate juvenile safety studies for treprostinil are not required.

During the SA in 2016, the Phase 3 clinical plan was overall accepted. The CHMP stated, e.g., that the differences in the PK/PD should not only be statistically different, but also clinically relevant to support the claim that LY900014 is not a duplicate of insulin lispro. The non-inferiority margin (NIM) for EU was advised to be 0.3% (in accordance with Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, CPMP/EWP/1080/00 Rev. 1, 14 May 2012) even though the studies were planned for the FDA to use a NIM of 0.4%. Omitting separate studies in patients with renal and hepatic insufficiency was accepted during SA, as insulin lispro is a well-known active substance.

2.2. Quality aspects

2.2.1. Introduction

Liumjev (company code: LY900014) is an ultra-rapid-acting formulation of insulin lispro developed for subcutaneous (SC) and intravenous (IV) use to improve glycemic control in patients with diabetes mellitus (i.e. in adults with type 1 diabetes (T1D) or type 2 diabetes (T2D)).

Liumjev is presented as a solution for injection containing 100 or 200 units/mL of insulin lispro as active substance. Other ingredients are: glycerol, magnesium chloride hexahydrate, metacresol, sodium citrate dihydrate, treprostinil sodium, zinc oxide, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections (WFI).

Liumjev is available in a vial, cartridge or prefilled pen: in a 10 ml vial, in a 3 ml cartridge for use in re-usable pens and in a 3 ml disposable pre-filled pen injector 100 units/mL and 200 units/mL (only for prefilled pen). The prefilled pens where cartridges are sealed in a disposable pen injector are called the "KwikPen" or "Junior KwikPen". The pen injector is designed to deliver multiple doses of variable volume (each KwikPen delivers 1-60 units in steps of 1 unit in a single injection and each Junior KwikPen delivers 0.5 - 30 units in steps of 0.5 units in a single injection).

2.2.2. Active Substance

Liumjev is a new formulation of insulin lispro and contains the same active ingredient (INN: insulin lispro) as used in the Humalog (EMEA/H/C/000088) family of products.

Insulin lispro is a human insulin analogue produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. All the development of Liumjev was done with insulin lispro active substance (AS) that is currently approved in the EU market for use in Humalog. The information for the active substance presented in Module 3 aligns with the information previously provided to support the Humalog marketing authorization.

General Information

The active substance insulin lispro is a known active substance produced by recombinant DNA technology utilising a non-pathogenic laboratory strain of *Escherichia coli* (*E. coli*). Insulin lispro is a 2-chain peptide containing 51 amino acids and a molecular weight of approximately 5808 amu. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. Insulin lispro is identical in structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B chain. Human insulin is Pro(B28), Lys(B29), whereas insulin lispro is Lys(B28), Pro(B29). As in human insulin, insulin lispro contains two interchain disulfide bonds and one intrachain disulfide bond. A representation of the primary structure of insulin lispro is shown in the Figure 1.

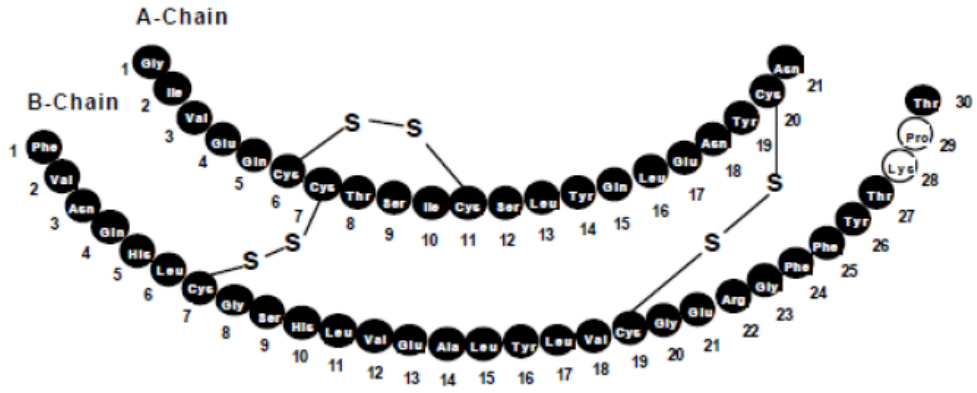


Figure 1. Insulin Lispro Primary Structure

Manufacture, process controls and characterisation

Manufacturing process and process controls

The active substance manufacturing process consists of a fermentation process stage and a purification process stage. The fermentation broth is harvested, homogenized, and the gene product is isolated.

The purification process for insulin lispro is divided into several processing steps of initial purification, enzymatic transformation, final purification, and crystallization.

The active substance manufacturing process has been described in sufficient detail and supported by flow charts. The critical process parameters (CPPs) and intermediate specifications for the purification and fermentation processes are clearly indicated and are acceptable. Information regarding composition of

media, materials and equipment used, column/membrane regeneration/cleaning procedures and column lifetime is considered sufficient.

Manufacturing process development, control strategy and process validation

The control strategy for the insulin lispro process is based on a planned set of controls to ensure active substance product quality. Based upon risk assessments, process characterization and development, studies were performed to investigate parameters within, and beyond, ranges specified in the commercial-scale manufacturing batch records. The general approach to process development and determination of the overall control strategy is considered acceptable. Based on the development results presented, the proposed proven acceptable ranges (PAR) for the CPPs are considered supported and justified.

Process validation (PV) batches are manufactured using the registered process at the intended manufacturing scale and using qualified equipment. The fermentation, isolation and purification process steps are validated including several batches. The results obtained were within the established specified limits for all applicable critical process parameters, intermediate specifications, and active substance specifications. Furthermore, removal of process related impurities was validated. Data from several active substance process validation batches were collected and all parameters met the established comparability limits. The overall validation data are clearly presented and acceptable. It can be concluded that the active substance manufacturing process is consistent and operates within the established parameters.

Control of materials and cell banking system

Raw materials used during the active substance manufacturing are considered satisfactory for use in the commercial active substance manufacturing process.

The MCB and first WCB were cryopreserved. The requirements of the cell banks were accepted in the MAA of Humalog in 1996 and the insulin lispro has been produced using these cell banks ever since. A protocol is in place for generating future working cell banks.

Characterisation

Insulin lispro is a compendial active substance with a well-known structure. The structural elucidation work was performed and was repeated when the active substance purification process was changed. In addition, several independent *in vitro* assays were conducted to analyse the functional activity of the active substance. These assays also showed that biological activity of the active substance was not altered upon introducing some changes to the purification process. The characterisation studies presented are considered acceptable. Furthermore, purity and impurities were also addressed in compliance with the requirements of Ph. Eur. monograph no. 2085 "insulin lispro". Particular attention was made to identification and removal of AS-like variants and process-related impurities (potentially) introduced during the active substance manufacturing process. These impurities are shown to be reduced to acceptable low levels.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

The specification of insulin lispro active substance has been established based on its respective Ph. Eur. monograph no. 2085 "insulin lispro" and relevant ICH guidelines, quality of the active substance used in toxicological and clinical testing, active substance stability, and analytical method variability.

The proposed tests and acceptance criteria for routine active substance release are acceptable.

Analytical procedures

Adequate descriptions of analytical methods, including their system suitability criteria and evaluation have been provided. All non-compendial analytical methods are described in sufficient detail and properly validated according to ICH Q2 guideline. All analytical methods are considered suitable for the control of the active substance.

Batch analysis

Results from several full-scale process validation batches of insulin lispro active substance have been provided in the dossier. All proposed specifications were met. Batch-to-batch consistency is also demonstrated across all batches.

Reference standards

The Applicant uses a two-tier system and has provided sufficiently detailed information on the standards used up to date. Each lot of Reference Standard was qualified according to a subset of release tests as well as additional characterisation tests. The results presented are considered satisfactory.

Container closure system

Insulin lispro AS is stored in Ph. Eur. Type I amber glass vials with screw-cap lids having a liner of polytetrafluoroethylene (PTFE)-coated silicone. Sufficient information including the description of the material of each component, technical drawings and compatibility have been provided.

Stability

The stability studies cover those attributes from the active substance specifications that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy.

Insulin lispro active substance should be stored frozen in tightly capped containers, which are protected from direct light. The analytical procedures used to test the stability-indicating parameters are the same as those used for batch release. The acceptance criteria for stability are the same as described in the active substance release specifications.

Several process validation batches of active substance were placed on long term stability. In addition, accelerated stability data were generated. All long-term stability studies meet the specification limits through the proposed shelf life. Accelerated stability results indicate slight increases in total related substances. A post-approval stability protocol at long-term storage conditions is given. As no trends in the stability of insulin lispro is observed during the long-term stability studies, the claimed shelf-life can be accepted.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Liumjev finished product is a sterile finished product that is composed of insulin lispro (active substance) with treprostinil sodium, sodium citrate dihydrate, zinc oxide, magnesium chloride hexahydrate, metacresol, glycerol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections (WFI). The excipients have been justified based on formulation development studies and are in compliance with Ph. Eur. and USP, except treprostinil which has no compendial monograph. No novel excipients were used.

Liumjev is available in two concentrations 100 units/mL (U-100) and 200 units/mL (U-200). The 100 units/mL dosage strength will be dispensed in 10 mL vials and 3 mL cartridges for assembly into prefilled pen injectors or packaged into blister for use with re-useable insulin pen devices. The 200 units/mL dosage strength will be dispensed in 3 mL cartridges for assembly into the prefilled pen injectors only.

The product is presented as:

- 3 mL cartridge of 3 mL nominal volume of finished product solution which is irreversibly assembled into a disposable pen. The KwikPen disposable injector is a multi-use fully mechanical device intended to deliver a dosage range between 1 and 60 U in increments of 1 unit and doses from 0.5 to 30 units in increments of 0.5 units. The cartridge is composed of Ph. Eur. glass type I closed with a halobutyl rubber plunger stopper and a sealing disk of halobutyl rubber in compliance with Ph. Eur.
- 3 mL cartridge of 3 mL nominal volume of finished product solution which is to be used with marketed reusable Lilly pen injectors.
- 10 mL vial containing 10 mL nominal volume of finished product solution to be administered by use of a syringe, a pump device or to be diluted in an infusion bag. The Ph. Eur. type I glass vials are closed using halobutyl elastomeric closures (stopper). The closures are secured in place using an aluminum/polypropylene, flip-top seal.

Liumjev finished product involves the use of a micro-dose of treprostinil (delivered as treprostinil sodium) as an excipient to enhance the absorption of insulin lispro by local vasodilation, rather than an active pharmaceutical ingredient to elicit a systemic effect. The microdose concentration (1 µg/mL in the Liumjev formulation) of treprostinil is consistent in both the 100 units/mL and 200 units/mL strengths.

Formulation development

The Quality Target Product Profile (QTPP) along with the critical quality attributes (CQAs) were used to guide the formulation stability. The formulation development strategy was to develop the Liumjev finished product formulation with faster insulin lispro action than Humalog Injection and with a finished product stability profile similar to Humalog.

All inactive ingredients (excipients) meet compendial requirements with the exception of treprostinil sodium. The choice of excipients as well as their concentrations are considered justified from a quality point of view.

Manufacturing process development and comparability assessment

Elemental impurities are monitored as required in ICH Q3D guideline. A summary of the risk assessment was provided. The manufacturing process development section is considered satisfactorily described.

The Liumjev finished product critical quality attributes (CQAs) were defined early during the development process. Several moderate and high-risk unit operations were identified.

Filtration and filling operations have been sufficiently presented.

The manufacturing process has been validated at the proposed commercial scale.

Container closure system

The choice of the packaging components as described above is considered justified. All primary packaging components comply with the relevant Ph. Eur. monographs – the dimethicone used for siliconization complies with the Ph. Eur. monograph on *Silicone oil used as a lubricant*.

The Liumjev KwikPen 100 units/mL, Liumjev KwikPen 200 units/mL and Liumjev Junior KwikPen 100 units/mL are dial-and-dose pen injectors, intended for SC (self-) administration of the insulin lispro formulation. They are all based on existing (Junior) KwikPen platforms. The KwikPen delivers 1 – 60 units in steps of 1 unit in a single injection, whereas the Liumjev Junior KwikPen delivers 0.5 – 30 units in steps of 0.5 units in a single injection. The latter is thus suitable for patients who may benefit from finer insulin dose adjustments. Since the Liumjev pre-filled pens are single-use, multi-dose delivery devices, there is no assessment by a Notified Body for CE mark.

Sufficient design verification testing, human factors and risk assessment were performed to ensure proper functioning of the pre-filled pen injector device. The cartridge presentation, which is only available for the 100 units/mL dosage strength, is for use with Lilly re-usable pens. The dosing accuracy of the re-usable pens has been appropriately demonstrated.

Microbiological attributes have been appropriately addressed in order to sustain the finished product sterile. Container closure integrity test for cartridge and vial has been appropriately demonstrated. Furthermore, metacresol is added to the formulations to inhibit microbial growth in accordance with Ph. Eur.

Manufacture of the product and process controls

The concentrations and presentations are the same as those currently approved for Humalog in the EU. The Liumjev 100 units/mL and 200 units/mL concentrations development was done concurrently. The only differences in the concentrations are the amount of insulin lispro and zinc, all other excipient concentrations are the same. The vials and cartridges are manufactured in the same facilities as those used for Humalog and the manufacturing processes are aligned to the Lilly insulin platform.

Batch formula has been presented for the proposed commercial scale.

The manufacturing process description/flow chart has been sufficiently presented, describing the main processing steps; finished product solution preparation, bioburden reduction filtration, sterilizing filtration and aseptic filling in cartridges and vials.

Process controls

Acceptance criteria for controls are provided for the parameters/controls that have been determined to be critical to ensure that the CQAs are met. The criticality assessment is performed carefully during pharmaceutical development studies and definitions for process parameters and process controls are given. The microbiological control of the finished product manufacturing process has been appropriately addressed.

Process validation

The process validation (PV) was performed with several commercial scale batches and includes process validation, sterilisation process validation and shipping validation. PV data have been presented. Sufficient validation data on the pre-filled pen assembly has been provided.

Product specification, analytical procedures, batch analysis

Specification

Commercial specifications for insulin lispro finished product are established based on historical knowledge from Humalog family of products, clinical batches, formulation development, and potential risk of impact on CQAs with regards to patient safety, and stability of finished product.

The specification for the finished product includes identity, potency, purity, sterility, bacterial endotoxins. The proposed tests and acceptance criteria are acceptable.

The proposed specifications are considered justified and acceptable.

Analytical procedures

The analytical methods are validated successfully in accordance with ICH Q2 guideline. The validation results were acceptable and showed that the analytical methods are suitable for their intended use and valid for the new formulation.

Batch analysis

Batch analyses results of several commercial scale batches, were presented showing consistent results. Additional results from primary stability and clinical batches demonstrate consistency between the manufactured batches.

Reference standards

The same reference standard is used as for the analysis of the active substance. This is acceptable.

Container closure system

The Liumjev finished product is supplied in Type I glass cartridges and vials and prefilled pen. The cartridge is sealed at the bottom with an elastomeric plunger and at the top with a disc seal consisting of a bilayer elastomeric disc and an aluminium shell. The vials are closed with a halobutyl elastomeric stopper secured with an aluminum flip-top seal.

The Liumjev pre-filled pens and Humalog pens are functionally the same. The device constituent components of the two pens differ only by external component colours; all internal parts are shared. The different components of the primary packaging comply with the corresponding Ph. Eur. requirements. In addition, the used elastomeric components are latex free.

Stability of the product

A shelf life of 24 months for the finished product is proposed. Liumjev finished product should be stored in a refrigerator between +2 °C and +8 °C, protected from light. After first use, it can be stored at room temperature protected from light for up to 28 days.

The stability studies are conducted according to the relevant stability guidelines, ICH Q5C, ICH Q1A and ICH Q1B.

Real time data is available for clinical scale batches as well as for process validation batches that are representative of the commercial process. The acceptable shelf life has been assessed based on the data presented for the primary stability batches and process validation batches given that comparability has been demonstrated between primary stability and process validation batches.

Primary stability studies used a commercially representative manufacturing process.

In-use stability testing is performed with batches at multiple time points during the real-time storage. The data supports the storage of the in-use finished product (after the disc seal has been punctured) unrefrigerated for up to 28 days at a maximum temperature of 30°C for pen injectors and 9 days in a pump reservoir.

In photostability testing, the product was demonstrated to be light sensitive and hence the product should be protected from light. The secondary packaging was proven sufficient to protect the product from light.

At the recommended storage (real-time) condition of 2°C to 8°C, all available results have remained within the proposed shelf life acceptance criteria. Based on the primary stability data, as well as the supporting stability studies, the claimed shelf life of 24 months is acceptable for the cartridge and vial presentations. The claimed after first use shelf life of up to 28 days when stored at room temperature and protected from light is also acceptable.

Chemical, physical in-use stability after dilution with dextrose 50 mg/ml or sodium chloride 9 mg/ml solutions for the vial presentation has been demonstrated for 14 days at 2–8 °C and 28 hours at 20-25 °C when protected from light. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions. For pump devices it is recommended to change the Liumjev U-100 in the pump reservoir at least every 9 days.

Medical device

The 3 mL cartridges are assembled in prefilled pen injectors (U-100 with 1-unit and 0.5-unit increments; U-200 with 1-unit increments) using the same injector device platform as the finished products Humalog and Basaglar. A detailed description of the pens and device constituents has been provided. The device constituent components were developed and evaluated according to procedures that comply with the design control principles required by EN ISO 13485:2016 ("Medical devices – Quality Management Systems – Requirements for regulatory purposes").

Device performance and compliance to ISO 11608-1:2014 ("Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems") was assessed for system designation C.

Sufficient biocompatibility testing, design verification testing (including design differentiation), risk management and human factors evaluation were performed according to the relevant ISO norms to ensure proper functioning of the device.

Adventitious agents

Considering that the manufacturing takes place in *E. coli*, no formal viral clearance studies are needed.

A TSE Declaration has been provided stating that no materials of animal origin are utilized in the insulin lispro active substance manufacturing process or in the manufacture of the finished product.

The adventitious agents safety evaluation is considered satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Liumjev finished product supplied in 10 mL vials and 3 mL cartridges is intended for SC and IV administration. The formulation differs from Humalog with the functional active excipients. The excipients

meet the requirements of Ph. Eur., USP and NF except for treprostinil, which has been described more carefully and in adequate detail. The cartridges are used in combination with a disposable pen (integrated drug-device combination) or in combination with reusable pen injectors. Vials may be used for continuous subcutaneous insulin infusion with insulin pumps. For infusion administration, vials can be diluted in dextrose 50 mg/mL or sodium chloride 9 mg/mL solutions.

The overall quality documentation provided for Liumjev in the marketing authorisation application is of adequate quality. No major objections were identified during the assessment. There is a good control strategy in place to guarantee consistent quality of the finished product. The overall quality of Liumjev is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the data provided, marketing authorisation application for Liumjev is considered approvable from a quality point of view.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacology data of insulin lispro available as a part of the development of Humalog is used to bridge the pharmacology data of LY900014. The concentration of active substance is identical to Humalog, with the addition of two excipients, sodium citrate and treprostinil, which aim at accelerating the absorption at the site of injection by increasing blood vessel permeability (sodium citrate) and vasodilatation (treprostinil). LY900014 contains 1 µg/ml treprostinil and 15 mM sodium citrate, as well as 5 mM $MgCl_2$, the other excipients are similar between Humalog and LY900014 (with the exception of Dibasic sodium phosphate heptahydrate present only in Humalog). All non-clinical studies conducted with insulin lispro alone (prior to 1996) have been previously reviewed during the initial marketing application for Humalog. No separate pharmacology studies have been conducted with LY900014, but the effects on plasma glucose levels in comparison to that of Humalog was measured as part of a PK/PD study in diabetic swine model.

New pharmacology data included the primary pharmacodynamics studies of the effects of citrate (transendothelial cell transport and vascular permeability) and treprostinil (local changes in blood flow) alone or in combination with insulin lispro (evaluation of the accelerated time of action of the glucose lowering effect), and safety pharmacology studies with treprostinil alone.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The bioavailability, bioeffectiveness, and mechanisms of action of insulin lispro were assessed as part of development of Humalog in a series of *in vitro* and *in vivo* experiments. The total glucodynamic effects of

insulin lispro were indistinguishable from human insulin after subcutaneous administration in rats, dogs, rabbits and pigs. The pharmacodynamics of insulin lispro is well known and is same in LY900014, only the onset of the effects are expected be different due to the new formulation.

LY900014 includes two excipients treprostinil and sodium citrate (henceforth 'citrate'), with independent mechanisms to accelerate the absorption of insulin lispro resulting in a faster insulin time-action profile when compared to Humalog. Treprostinil is a prostacyclin analogue that increases blood flow at the injection/infusion site through local vasodilation. Citrate promotes vascular permeability. The effects of citrate were assessed *in vitro* in the transendothelial cell transport assay and *in vivo* in the vascular permeability assay in rats. Transport of insulin lispro across the human dermal microvascular endothelial cell layer was increased in the presence of citrate alone (15 mM, 25 mM or 35 mM) or citrate (25 mM or 35 mM) and 5 mM MgCl2 together in comparison to the PBS buffer control. The increase in transport was 1.9-fold with 35 mM citrate. In *in vivo* rat vascular permeability assay (Miles assay) it was demonstrated that 25 mM citrate significantly enhanced vascular permeability. Local changes in blood flow due to SC injection of treprostinil were assessed in rats using dermal Laser Doppler Imaging. In this assay, it was demonstrated that 0.1 ng - 40 µg treprostinil induced local vasodilatation.

The proof of concept of function of sodium citrate and treprostinil excipients to facilitate the faster lowering of plasma glucose levels was demonstrated in the studies in diabetic miniature Yucatan swine. Due to similarities of skin and subcutaneous tissue of miniature swine and humans, diabetic (alloxan treated-insulin deficient) miniature Yucatan swine is considered a representative model to determine efficacy, potency, and time of action for subcutaneously delivered insulin molecules/mixtures. Study DBT253 was conducted with the final commercial formulation of LY900014 (Figure 2 and Table 1). Lowering of the serum glucose levels was rapid after the SC administration of LY900014. LY900014 lowered the plasma glucose levels significantly faster at early time points *i.e.* 10 and 15 minutes, with p=0.0001 and p=5.76E10-05, respectively, compared to Humalog. After 30 minutes, the effects of LY900014 and Humalog on lowering of the glucose levels were similar.

Figure 2. Average serum glucose change from baseline (before SC administration up to 360 min following SC dosing); comparative study with insulin lispro and LY900014.

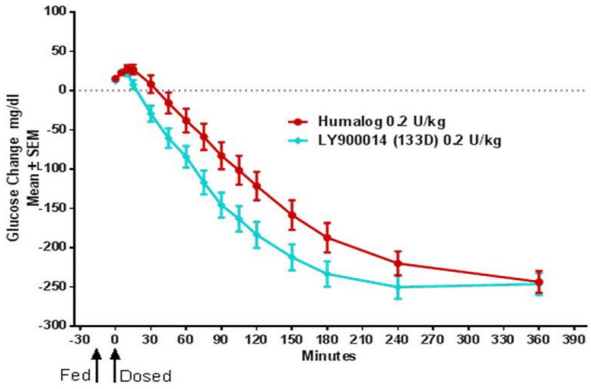


Table 1. Average serum glucose change from baseline of diabetic swine treated with Humalog or LY900014.

Time (minutes)	Serum Glucose (mg/dL)			
	Humalog		LY900014	
	Mean	SEM	Mean	SEM
-30	322.1	5.7	341.6	8.6
-20	327.6	7.5	349.2	9.8
0	338.3	8.0	357.7	9.3
5	345.7	7.8	369.6	9.7
10	351.1	8.6	371.9	10.1
15	349.9	10.0	352.8	11.0
30	331.3	14.4	315.9	13.2
45	307.4	16.4	288.6	14.4
60	284.9	18.2	260.9	14.4
75	264.2	19.8	228.4	14.8
90	240.2	19.7	199.6	14.5
105	223.1	20.7	182.1	15.0
120	201.6	19.5	161.8	15.1
150	164.7	19.7	133.2	14.7
180	135.8	19.3	111.9	16.0
240	103.2	15.2	95.2	16.0
360	79.7	12.9	99.3	13.8

Abbreviations: SEM = standard error of the mean.

The additional *in vivo* data in swine treated with insulin lispro with various concentrations of sodium citrate with/without treprostinil was in line supporting the hypothesis of faster glucose lowering effect of the novel formulation components in comparison to Humalog.

Secondary pharmacodynamic studies

Secondary pharmacodynamics studies were not conducted with LY900014.

Safety pharmacology programme

The safety pharmacology studies including cardiovascular, respiratory, renal and central nervous system effects for insulin lispro were conducted as part of Humalog's non-clinical development. The observed effects were comparable to those produced by human insulin. No safety pharmacology studies have been performed with LY900014.

The safety pharmacology studies of treprostinil excipient included GLP compliant *in vitro* and *in vivo* studies. *In vitro* hERG and *in vivo* cardiovascular safety pharmacology studies caused QT/QTc prolongation in dogs. These results are in line with previously reported findings in dogs and humans, and are not due to blockade of hERG but an artefact of the rapidly changing heart rate that occurs in response to decreased blood pressure from treprostinil (Tyvaso, 2017). The NOEL for cardiovascular effects in the dog studies was 4 µg/kg (49.4x the C_{max} of the highest tested treprostinil dose of 1500 ng in human subjects). The cardiovascular effects at the higher doses (≥0.015 mg/kg) noted in the dog studies is unlikely cause for a safety concern for patients with diabetes; the microdoses of treprostinil is used in LY900014 (≤5 ng/kg, 3 times daily). The CNS/neurobehavioral safety profile of treprostinil was assessed in rats as part of the 3 months repeated dose toxicity study. Neurological (CNS/behavioural evaluation and body temperature measurements) and respiratory examinations following a single SC injection of treprostinil did not show any important changes in CNS or respiratory function (investigated by plethysmography) at doses up to 0.1 mg/kg/day, the highest dose tested. In the Functional Observation Battery (FOB) tests, treprostinil did not induce neurobehavioural effects. The NOELs for respiratory and CNS endpoints were 0.1 and 0.03 mg/kg/day, respectively.

From the non-clinical perspective, no further action is necessary with respect to safety pharmacology. The potential for adverse safety pharmacological events at clinical treprostinil doses is considered unlikely.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not conducted with LY900014.

2.3.3. Pharmacokinetics

As part of the Humalog submission, a series of studies to analyse the pharmacokinetics of insulin lispro was performed. The pharmacokinetics of insulin lispro were studied in both rats and dogs. These studies are not re-evaluated in this data review. Insulin lispro's pharmacokinetics is well known; it is rapidly absorbed and degraded to small peptide fragments and amino acids. After absorption, the active substance insulin lispro behaves in the same way as with Humalog. New pharmacokinetic studies include combined PD/PK study evaluating effects of various fast acting LY900014 formulations in diabetic Yucatan miniature swine, and the ADME and toxicokinetic studies with treprostinil as part of the repeated-dose and embryofetal developmental toxicity studies in rat, dog and rabbit. The ADME characteristics of other excipients citrate and magnesium chloride were not evaluated, as these are approved pharmaceutical excipients.

Validated bioanalytical LC-MS/MS methods were used to measure treprostinil in toxicokinetic evaluations. Qualified "fit for purpose" radioimmunoassay method was used to quantify total insulin in plasma of diabetic swine.

Absorption

The proof of concept of a more rapid absorption of insulin lispro in LY900014 in comparison to Humalog was shown *in vivo* in miniature Yucatan diabetic swine in the PD/PK single dose studies. Subcutaneous delivery of LY900014 commercial formulation resulted in faster absorption of insulin lispro in diabetic swine in comparison to Humalog. The mean early 50% t_{max} decreased from 29.7 minutes (Humalog group) to 12.9 minutes (LY900014 group), with a p-value of 0.0002. The mean late 50% t_{max} decreased from 169 minutes (Humalog group) to 129 minutes (LY900014 group), with a p-value of 0.011. Consistent with faster absorption of insulin lispro, a more rapid decrease in plasma glucose levels (within 5 - 15 minutes) with LY900014 was demonstrated.

Absorption of treprostinil was analysed in rats after a single 0.4 mg/kg SC and 0.2 mg/kg IV dose of [^{14}C]treprostinil. [^{14}C]treprostinil was rapidly absorbed with a t_{max} of 0.25 hours. The mean systemic exposure of treprostinil accounted for 37% of the circulating radioactivity after both SC and IV administrations. The half-life ($t_{1/2}$) for treprostinil was less than 2 hours after SC dosing.

Distribution

The tissue distribution of LY900014 or insulin lispro in the novel formulation including treprostinil and sodium citrate, was not studied. It is expected that the presence of the excipients treprostinil and sodium citrate would not change the rapid clearance of insulin lispro by the liver and kidney, or affect the overall tissue distribution of that known for Humalog. No studies were conducted to address plasma protein binding and placental transfer of insulin lispro, LY900014 or treprostinil, and are not required.

Treprostinil was widely distributed in tissues and organs in male pigmented and non-pigmented rats. Highest amounts of treprostinil-related radioactivity were detected at the dosing site, plasma and the clearing tissues liver and kidney. This distribution pattern is not considered to change the LY900014 distribution in comparison to Humalog. Treprostinil does not bind to melanin. Elimination was near complete by 48 hours post dose. High treprostinil exposure was achieved in rats, rabbits, and dogs with

high margin of safety for clinical microdoses (NOAELs 462-fold to 1121-fold in rats and dogs, 1452-fold in rabbits). Exposure increased dose proportionally. No accumulation was observed.

Metabolism

The metabolic pathways are known for LY900014's active ingredient insulin lispro, which is a biological pharmaceutical and is degraded to small peptides and amino acids. No further studies are required with LY900014 alone. The earlier data of metabolic profiling of treprostinil (Remodulin) was investigated in bile collected from rats given single, oral and IV 200 µg/kg doses of [^{3}H]-treprostinil. The chemical data and the *in vivo* data from the rat, dog and human confirmed that treprostinil is a chirally pure drug substance and does not undergo chiral inversion *in vivo,* and undergoes extensive metabolism to more polar compounds.

Metabolite profiling was conducted in rat and human hepatocytes *in vitro* following incubation with [^{14}C]treprostinil for up to 4 hours, and *in vivo* in rats following a single SC 0.4 mg/kg dose of [^{14}C]treprostinil. The major treprostinil metabolism pathways involved oxidation at various sites on the molecule, including a combination of hydroxylation and dehydrogenation. Treprostinil was extensively metabolised; 26 metabolites were detected *in vitro* and 22 *in vivo*. The major *in vivo* metabolism pathways for treprostinil in rats were similar to those observed *in vitro*. All metabolites found in human hepatocytes were identified in rat hepatocytes. In human hepatocytes, the major metabolites were M7, M18 and M2 (16%, 9%, and 9%, respectively). The major metabolites were M18 and M17 (49% and 10%, respectively) *in vitro* in rat hepatocytes and M18 (18%), M10 (12%), M3 (10%), M21 (7%) and M15 (5%) *in vivo* (rats). Although the metabolism was studied only in rats and no data were presented from the other toxicity species i.e. rabbits and dogs, the data provided are considered sufficient due to the existing knowledge of the inter-species comparative metabolism.

Although not examined in these experiments, treprostinil has been shown be a major substrate for CYP2C8 and to a minor extent CYP2C9 *in vitro*.

Excretion

No new excretion studies were conducted with LY900014 or insulin lispro. Insulin lispro undergoes extensive proteolysis into small peptide fragments and amino acids. In rats, the majorityof the insulin lispro was eliminated via the urine (78.7%), with a minor amount eliminated via the faeces (3.77%). The major route of treprostinil excretion was hepatobiliary/faecal elimination of metabolites.

Pharmacokinetic drug interactions

Pharmacokinetic drug interaction studies were not conducted. Studies are not warranted for recombinant proteins per ICH S6(R1). No interactions are expected with treprostinil due to its low plasma concentrations, and hence no pharmacokinetic drug interaction studies are warranted.

2.3.4. Toxicology

A full nonclinical safety programme was conducted for insulin lispro to support the marketing authorisation for Humalog (in 1996). Findings were related to the mode of action or exaggerated pharmacology of insulin, and no findings of toxicological concern were observed.

New toxicology studies with insulin lispro evaluated the injection site tolerability of Humalog (insulin lispro solution, injection) and Remodulin (treprostinil injection, solution), alone or in combination (a representative Phase 1 formulation) by SC injection to rats. Other new toxicity studies are focused on the

evaluation of the safety of treprostinil excipient alone and include repeated-dose toxicity studies in rats and dogs, fertility studies in rats, embryo-foetal studies in rats and rabbits, and a pre- and postnatal development study in rats.

LY900014 includes treprostinil, sodium citrate and magnesium chloride as excipients. Sodium citrate and magnesium chloride are common excipients and require no further safety studies in amounts used in the LY900014 formulation. Treprostinil's safety was assessed extensively in the preclinical species.

Single dose toxicity

No single dose toxicity studies were conducted for LY900014 or treprostinil.

Repeat dose toxicity

No specific repeated dose toxicity studies have been conducted with LY900014, as studies have been conducted with Humalog. In chronic toxicity studies with insulin lispro, lowering of blood glucose was accompanied by changes in serum lipids and body weight gain. The repeat-dose toxicity of treprostinil was evaluated in 13-week subchronic toxicity studies in pharmacologically relevant species: the rat, dog, and in pregnant rabbits. Treprostinil was administered daily by subcutaneous injection to match the route of administration in the clinical program.

Treprostinil was well tolerated in 6 months repeated dose toxicology studies in rats and dogs. The main clinical observations with treprostinil treatment were related to transient vasodilatory pharmacological effects in both of the species. There was no indication of direct target organ toxicity in either rats or dogs. In contrast to the Applicant's conclusions that there was no evidence of injection-site reactions to treprostinil, injection site reactions were reported. Injection site reactions included minimal to moderate vascular degeneration/necrosis, minimal to slight degeneration/necrosis of the panniculus carnosus muscle, slight to moderate subcutaneous haemorrhage, and minimal inflammation. Other effects included transient reddening of skin and pinna, transient decreased systolic and pulse pressures with increases of heart rate and trend of a shorter QT interval on Day 85 or 177 of dosing in dogs, body weight decreases and changes in platelets, white blood cells reticulocyte, neutrophil, and monocyte counts in rats (determined as mild). The skin and cardiac effects were resolved within 1 hour in rats, and 1.5 hours in dogs post-dosing. These findings are consistent with the main effects observed after continuous SC or IV delivery of treprostinil in toxicity studies previously included in the Remodulin dossier (swelling at the infusion site, redness of skin, decreases in body weight and haematological changes).

The maximum tolerated dose was exceeded in pilot studies; in rats, the MTD was 0.6 mg/kg/d, which resulted in cardiac lesions and hypoactivity and in dogs 0.28 mg/kg/d, which resulted in hypoactivity, and clinical signs of pronounced vasodilatation at 30 - 45 min post-dose (salivation, pale mucous membranes, increased capillary refill, bradycardia) and vomiting.

NOAEL in rats was 0.1 mg/kg/day and in dogs 0.07 mg/kg/day providing the high safety margins i.e. 1121x (rats) and 565x (dogs) relative to the maximum expected daily dose of treprostinil in 1.5 U/kg/day of LY900014 in patients with T2D. At these NOAELs the exposure multiples greatly exceed the ICHM3(R2) threshold of 50x max human exposure.

Genotoxicity

Insulin lispro was negative in a full range of standard tests of genotoxicity, which included bacterial mutation tests and *in vitro* and *in vivo* mammalian systems. No specific studies have been conducted with LY900014. Treprostinil was not genotoxic according to standard battery of genotoxic tests, in Ames assay

(up to dose of 5000 µg/plate), chromosome aberration test in CHO cells and in *in vivo* in rat bone marrow cells micronucleus assay. These results are in line with the previous studies of treprostinil indicating lack of genotoxic potential (Remodulin EPAR: treprostinil has not been genotoxic in *in vitro* and *in vivo* assays).

Carcinogenicity

No carcinogenicity studies have been conducted with insulin lispro, LY900014 or treprostinil.

Reproduction Toxicity

Insulin lispro demonstrated no teratogenic or reproductive effects. Reproductive and developmental toxicity studies have not been conducted with LY900014. Reproductive and developmental toxicity studies with treprostinil included fertility studies in rats, embryo-foetal studies in rats and rabbits, and a pre- and postnatal development study in rats. No unexpected findings were noted in these studies.

Clinical signs in reproductive and development toxicity studies in rats and rabbits were limited to transient, dose-related flushing of the extremities secondary to the vasodilatory pharmacology of treprostinil and irregular respiration and hypoactivity in rats at 0.1 mg/kg/ day doses.

Fertility and early embryonic development studies with treprostinil were conducted in rats. Treprostinil had no effects on the fertility. There were no adverse effects of treprostinil on sperm morphology, oestrus cyclicity, mating, fertility, conception, implantation, and embryonic survival at doses up to 0.1 mg/kg/day. NOAEL for male fertility and paternal toxicity was 0.1 mg/kg/day (746x relative to the maximum expected daily dose of treprostinil in 1.5 U/kg/day of LY900014 in patients with T2D). NOAEL for female fertility and maternal toxicity was 0.1 mg/kg/day (528x exposure margins in comparison to maximum human AUC).

Embryo-foetal development studies indicated that treprostinil was not teratogenic in rats at doses up to 0.1 mg/kg/day (NOAEL, 736x the maximum anticipated human AUC), or in rabbits at doses up to 0.4 mg/kg/day (NOAEL, 9136x the maximum anticipated human AUC). NOAEL for rat maternal toxicity was 0.1 mg/kg/day and rabbit 0.05 mg/kg/day corresponding to 726x and 1452x the maximum anticipated human AUC, respectively.

In the prenatal and postnatal development study in rats, there was no evidence of F0 maternal toxicity or adverse effects on F1 offspring growth, behaviour, and reproduction at doses up to 0.1 mg/kg/day (462x the maximum anticipated human AUC). The only noted effects were decrease in body weight gain and food consumption in rats at the highest dose tested i.e. 0.1 mg/kg/day, and a slight increase of the duration of gestation (22.9 days vs 22.5 days in the control group). This had no effect- on the viability of the rat foetuses or foetus weights, or other postnatal development endpoints. These results are in line with the earlier peri-/postnatal development study results with treprostinil administered by continuous SC infusion via osmotic pump (at 450 ng/kg/min) to rats in support of the registration for Remodulin (in these studies, there were no alterations in gestational length, number of implantation site per litter, or number of lost post-implantation, and no development and growth variations observed).

Previous pregnant rabbit studies at maternal toxic doses of treprostinil revealed some evidence of increased foetal skeletal variations. There were no treprostinil-related foetal skeletal variations noted in the new studies conducted with high excess of the treprostinil doses compared to those in LY900014. In the dose-range finding study in rabbits with high dose of treprostinil, tendency for a slight increase in early resorptions (post-implantation loss) was noted. These findings in rats and rabbits collectively indicated, that the use of minute quantities of treprostinil in LY900014 is not of a toxicological concern during pregnancy.

The reproductive and developmental toxicity study findings have been stated as follows in the Humalog EPAR section 4.6 Fertility: 'Insulin lispro did not induce fertility impairment in animal studies (see section 5.3)' and section 5.3: 'Insulin lispro did not induce fertility impairment, embryotoxicity or teratogenicity in animal studies.' The same text is included in the proposed SmPC sections 4.6/fertility and 5.3/preclinical safety data of LY900014 and is deemed adequate.

Juvenile toxicity studies were not conducted with LY900014. Juvenile toxicity studies were not required for insulin lispro.

Toxicokinetic data

The plasma TK of treprostinil was determined in male and female rats administered with daily SC doses of 0.01, 0.03, 0.10 mg/kg of treprostinil as the sodium salt for 3 months and daily SC doses of 0.01 and 0.10 mg/kg of treprostinil as the sodium salt for 6 months. The plasma TK of treprostinil was determined in male and female dogs administered with daily SC doses of 0.004, 0.015, and 0.070 mg/kg of treprostinil as the sodium salt for 3 months, and daily SC doses of 0.004 and 0.070 mg/kg of treprostinil as the sodium salt for 6 months. Toxicokinetic parameters were calculated after dosing on Days 1, 90, and 180 in the 6-month study in both species. In the reproductive and developmental rat toxicity studies, similar toxicokinetic profile of treprostinil were generally observed in the 3 months and 6 months rat studies. For the toxicokinetic profiling of treprostinil on GD 7 and 19 in pregnant rabbits, treprostinil was administered daily with SC doses of 0.05, 0.14, and 0.4 mg/kg.

Adequate treprostinil exposures were obtained in repeated dose toxicity studies in all species (rat, dog and rabbit). Toxicokinetics was similar in both genders. The exposures ($AUC_{0\text{-}24h}$ and C_{max}) were roughly dose proportional in rats and dogs. The exposure differences between males and females were less than 2-fold. After SC injection, treprostinil exhibited a t_{max} value of 0.5 hour for rats and dogs and 0.5 - 1.1 hours for pregnant rabbits.

The margin of safety for clinical microdoses of the excipient treprostinil at the toxicological NOAELs for treprostinil ranged from 462-fold to 1121-fold in rats and dogs, and was 1452-fold in rabbits.

Local Tolerance

No local tolerance studies were conducted with LY900014 commercial formulation. Local tolerance was evaluated as part of the repeat-dose toxicity studies with insulin lispro to support the marketing authorisation of Humalog. Injection site inflammation with insulin lispro was observed only in the 1-year rat study in high dose excess of those used clinically, 20 and 200 U/kg/day.

Humalog and treprostinil (Remodulin) where administered alone or in combination (a representative Phase 1 formulation) by SC injection to male rats once daily for 14 days. Up to SC dose of 2160 ng Remodulin/kg with or without up to 201 U Humalog/kg once daily for 14 days was well tolerated. No compound-related irritation was observed in this study at the injection sites as measured by Draize dermal irritation scoring or during a macroscopic and microscopic pathology examination at study termination. In the repeated dose toxicity studies with treprostinil in rats, injection site reactions were reported and were considered to be related to the pharmacology of treprostinil. These findings were in line with the previous studies with SC administration of treprostinil to dogs conducted to support the Remodulin marketing authorisation (treprostinil doses of 100 or 200 ng/kg/min induced lesions around the infusion site).

Other toxicity studies

No other toxicity studies have been conducted with LY900014. The ocular and dermal irritation potential of treprostinil were assessed. In these studies, treprostinil had the potential for dermal and ocular irritation. Treprostinil is predicted to be a severe category I ocular irritant based on the bovine corneal opacity study and permeability assay. Treprostinil had potential for dermal irritation at a dose level of 2140 mg/kg (adjusted for potency) in rats.

2.3.5. Ecotoxicity/environmental risk assessment

The use of LY900014 in humans is not expected to result in a risk to environmental organisms. LY900014 is a novel formulation that contains the active ingredient, insulin lispro, with the prostacyclin analogue treprostinil among the excipients. Insulin lispro is not excreted intact from humans in significant quantities and any protein that is excreted is subject to degradation during sewage treatment. Therefore, insulin lispro will not enter the environment.

Since treprostinil is an active ingredient in other registered drug products, the environmental risk assessment (Phase I) was estimated for treprostinil and its use as an active ingredient in Remodulin followed by add-in value of use of treprostinil in the LY900014. The $PEC_{surface}$ water for treprostinil was estimated as 0.000015 µg/L. The overall predicted environmental concentration of treprostinil was calculated 0.000022 µg/L. The concentration of treprostinil predicted to enter the environment is lower than the action limit of 0.01 µg/L. Therefore, is unlikely to be a risk for the environment following patient use. Neither insulin lispro nor treprostinil should be classified as persistent, bioaccumulative and toxic.

In conclusion, the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, LY900014 (insulin lispro) is not expected to pose a risk to the environment. In addition, LY900014 contains prostacyclin analogy treprostinil as an excipient, which is not expected to increase the environmental risk of LY900014.

2.3.6. Discussion on non-clinical aspects

LY900014 contains the known active pharmaceutical ingredient insulin lispro, with an ultra-rapid-acting formulation including the excipients treprostinil and sodium citrate. Insulin lispro is the active ingredient in Humalog (Eli Lilly and Company). The majority of the studies with insulin lispro have been assessed during the Humalog marketing authorisation assessment (1996) and are used as bridging data for the LY900014 application. A comprehensive program of non-clinical studies including safety pharmacology, genetic toxicity, subchronic toxicity, chronic toxicity, and reproductive and developmental toxicity have been conducted to demonstrate the safety of the novel excipient treprostinil. Treprostinil is an active ingredient in other medicinal products (such as Remodulin, Tyvaso) and the previous pharmacology, pharmacokinetics and toxicology data with treprostinil exist. Microdoses of treprostinil will be given to patients. Systemic plasma exposure is expected to be minimal and, the margins of safety were large in chronic toxicity studies in rats and dogs (993x and 565x, respectively). Other excipients *i.e.* sodium citrate and magnesium chloride in the final commercial formulation are known excipients and were components of the vehicle control in the *in vivo* nonclinical safety studies. In the new studies, there were no unexpected safety risks identified of the use of treprostinil as an excipient in the formulation of LY900014. Consequently, no safety concerns were raised. The findings were in line with the earlier published treprostinil toxicology study findings.

The proof of concept studies to demonstrate the faster glucose lowering effect of the development formulations (including various concentrations of treprostinil and citrate) were conducted in a miniature Yucatan diabetic swine. One of the studies (study DBT253) was conducted with the final commercial

formulation of LY900014, which can be considered pivotal for demonstrating the nonclinical mode of action. Several other concerns were raised as part of the D120 LoQ related to this study and the rationale for selection of the final commercial solution. It was clarified that the non-clinical studies and the only experiment with LY900014 (study DBT253) was conducted in parallel with the Phase 1 studies. The combination of sodium citrate and treprostinil at the doses used in the commercial formulation was tested in ITRE at the same time/before the last porcine study.

Whilst the pharmacological effect (vasodilation and increased vascular permeability) of both excipients on their own was clearly shown, the rationale for combining them with insulin lispro at the proposed doses in the commercial formulation LY900014 appeared not entirely clear. On request, the Applicant further elaborated the pharmacological rationale for the combination of treprostinil and sodium citrate with insulin lispro. It could be concluded that the commercial formulation and one of the formulations containing similar doses of excipients (15 mM citrate and 0.5 µg/ml treprostinil) enhanced PK properties in regards to increase in exposure, earlier T_{max} and faster glucose lowering in comparison with insulin lispro on its own. The Applicant was asked to further elaborate the rationale for the addition of MgCl2 (5 mM) as an excipient in the LY900014 commercial solution. MgCl2 is not present in the formulation of Humalog. The Applicant clarified, that the rationale for the addition of MgCl2 was to increase stability of insulin lispro hexamers, to counteract the effect of sodium citrate (on reducing the physical stability of insulin lispro hexamers).

In study DBT253, lowering of the serum glucose levels was rapid after the SC administration of LY900014 (within 20 minutes of the meal). Significantly faster lowering of plasma glucose levels was noted at early time points *i.e.* 10 and 15 minutes, with p=0.0001 and p=5.76E10-05, respectively, compared to Humalog. However, only the box-plot and curves on glucose changes over the time with the statistical significance were provided by the Applicant in initial submission. Average serum glucose concentrations (mg/dl or mmol/L) and the change from the baseline with the variability range were subsequently submitted in accordance with the D120 LoQ. The conclusion (of faster glucose lowering effect of LY900014 in comparison to Humalog) remains. Further, the Applicant was asked to clarify the identical p-values of changes in glucose levels in comparison of various formulations in Studies DBT232 and DBT233. It was clarified, that identical p-values between the treatment groups are not the result of repetition of data but represent the false discovery rate -adjusted p-values. Thus, the conclusions of the statistical differences between the formulations at early time points in the studies DBT232 and DBT233 are valid.

A summary of method qualification was requested for the "fit for purpose" method used to quantify the total insulin in minipig plasma in the studies DBT 231, 232, 233, 253. It was clarified, that the method (commercial RIA kit repurposed to quantify insulin in pig serum) was qualified as part of study DBT231 and the range of quantification was 20 or 39 to 5000 pM. Most measures obtained were within this range. Although the inter-study quality controls did not cover the whole range of quantification, especially, the upper limit, the assay was considered sufficiently fit for the purpose.

2.3.7. Conclusion on the non-clinical aspects

The new non-clinical data demonstrated the faster lowering of the blood glucose levels (within 15 minutes) and faster absorption of insulin lispro after the SC administration of LY900014 in diabetic swine, and the use of treprostinil at safe concentrations as an excipient. Overall, no non-clinical major objections were identified for LY900014, and no open issues remain. The non-clinical data package is deemed adequate.

2.4. Clinical aspects

2.4.1. Introduction

Tabular overview of clinical studies

Table 2. Overview of Pivotal Phase 3 Clinical Studies Supporting the Application.

Study ID	Design, Comparator, Background Therapy	Treatment Duration	Primary and Key Secondary Endpoints	Patients Randomized
Phase 3 MDI Studies				
I8B-MC-ITRM[a, b] (PRONTO-T1D)	Randomized, treat-to-target, multinational, 3-treatment group, parallel, active-controlled study in adults with T1D. 2 Double-Blind Arms: LY900014 or Humalog dosed 0-2 minutes prior to start of each meal (Mealtime). Open Label Arm: LY900014+20; dosed 20 minutes after the start of a meal (Postmeal) Blinded CGM conducted in a subgroup of patients. *Basal Insulin During Study:* Insulin glargine 100 units/mL, once or twice daily; Insulin degludec 100 units/mL, once daily	1-week screening, 8-week lead-in, 26 week (open-label treatment) or 52-week (double-blind treatments) treatment period with 26-week primary endpoint, 4-week safety follow-up with up to 26-week follow-up[b] for patients with treatment-emergent insulin lispro antibodies not returned to baseline.	*Primary Objective (ITRM, ITRN):* The primary objective of this study was to test the hypothesis that LY900014 was noninferior to Humalog on glycaemic control (noninferiority 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. A NIM of 0.3% was also tested. *Multiplicity Adjusted Objectives:* *ITRM*: To test the hypothesis that LY900014 was noninferior to Humalog on improving glycaemic control (NIM=0.4% for HbA1c) when administered 20 minutes after the start of a meal (LY900014+20) (H5). A NIM of 0.3% was also tested. *ITRM and ITRN*: To test the hypothesis that LY900014 was superior to Humalog: -in controlling 1-hour PPG excursions (H2) (MMTT), when administered as prandial insulin at Week 26 - in controlling 2-hour PPG excursions (MMTT), when administered as prandial insulin at Week 26 (H3) -was superior to Humalog on improving glycaemic control when administered as prandial insulin (change from baseline to Week 26 in HbA1c) (H4). *CGM Sub-Study, (ITRM):* *Primary Endpoint:* Compare	LY900014: 451 Humalog: 442 LY900014+20: 329 *CGM Sub study* LY900014: 97 Humalog: 99 LY900014+20: 73
I8B-MC-ITRN[b] (PRONTO-T2D)	Randomized, treat-to-target, multinational, 2-treatment group, parallel, active-controlled study in adults with T2D. 2 Double-Blind Arms: LY900014 or Humalog dosed 0-2 minutes prior to start of each meal (Mealtime). *Basal Insulin During Study:* Insulin glargine 100 units/mL, once or twice daily; Insulin degludec 100 units/mL or 200	1-week screening, 8-week lead-in, 26-week treatment period, 4-week safety follow-up, with up to 26-week follow-up [b] for patients with treatment-emergent anti-lispro antibodies not returned to baseline.		LY900014: 336 Humalog: 337

Study ID	Design, Comparator, Background Therapy	Treatment Duration	Primary and Key Secondary Endpoints	Patients Randomized
	units/mL, once daily. *OAMs During Study*: Metformin and/or SGLT2 could be continued.		double-blind LY900014 and Humalog with respect to the $iAUC_{0\text{-}2hours}$ after breakfast obtained from up to 14 days of CGM use at Week 26.	
Phase 3 Continuous subcutaneous insulin infusion (Pump) Study				
I8B-MC-ITSI (PRONTO-Pump)	Randomized, double-blind, multinational, outpatient, 2-treatment group, crossover, active-controlled study in adults with T1D. Meal bolus doses of LY900014 and Humalog were delivered 0-2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.	1-week screening period, 2-week lead-in period followed by a 2-period crossover and a 4-week safety follow-up. Each crossover consisted of 6 weeks of treatment with no washout between periods.	Comparison with respect to the rate (events/patient/30 days) of infusion set failures that led to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycaemia with blood glucose >250 mg/dL (13.9 mmol/L) that did not decrease within 1 hour following a correction bolus delivered via the pump.	LY900014/ Humalog: 24 Humalog/ LY900014: 25

CGM = continuous glucose monitoring; **H** = hypothesis; **HbA1c** = hemoglobin A1c; **iAUC0-2hours** = incremental glucose area under the concentration versus time curve from time 0 to 2 hours; **MMTT** = mixed meal tolerance test; **NIM** = noninferiority margin; **OAM** = oral antihyperglycaemic medication; **T1D** = type 1 diabetes; **T2D** = type 2 diabetes .

a The 2 double-blinded arms in Study ITRM continued on to 52-weeks, and the patients from Japan enrolled in the open-label arm continued on to 52 weeks .

b The primary end-point evaluation for Studies ITRM and ITRN occurred at 26 weeks (database lock: [ITRM: 17 September 2018; ITRN: 17 August 2018]). . Study ITRM was planned as a 52-week study to meet FDA requirements (Section 2.5.1.4). Both studies have an ongoing 6-month anti-insulin lispro antibody follow-up assessment period per FDA request (Section 2.5.1.4). Both studies included a maximized extended enrollment addendum to support registration requirements in participating countries.

Table 3. Overview of Clinical Pharmacology Studies Supporting the Application.

Study	Description	Population (N)	Study Drug and Dose †
Study Evaluating Citrate			
F3Z-FW-ITCA (*ITCA*)	Part A: Effect of different concentrations of citrate on the PK of insulin lispro (compared to Humalog). Part B: Intra- and inter-subject PK variability of the selected insulin lispro formulation.	Healthy subjects (54)	Part A (N = 24): 35, 25, 15 mM citrate + 7.28 U insulin lispro versus 7 U Humalog Part B (N = 30): 25 mM citrate + 7.28, 15.47, or 30.03 U of insulin lispro
Studies Evaluating Treprostinil			
H9D-MC-ITAO (*ITAO*)	Part A: Local PD effect (injection-site blood flow), and PK of 6 SC dose levels of treprostinil compared to placebo Part B: PK and GD of insulin lispro when co-administered with 1 of 3 dose levels of treprostinil	Healthy subjects (26)	Part A: 4, 40, 120, 400, 1000, and 2000 ng of treprostinil or placebo Part B: 40, 400, or 2000 ng of treprostinil and 15 U insulin lispro or placebo and 15 U Humalog
H9D-FW-ITAQ (*ITAQ*)	Local PD effect (injection-site blood flow), and PK of 6 SC dose levels of treprostinil compared to placebo	Patients with T2D (8)	4, 40, 120, 400, 1000, and 2000 ng of treprostinil or placebo

Study	Description	Population (N)	Study Drug and Dose †
I8B-FW-ITRA (*ITRA*)	Comparison of PK and GD of 4 Test formulations of insulin lispro co-formulated with treprostinil.	Healthy subjects (28)	Treprostinil: 4, 40, 400, or 1000 ng with 15 U insulin lispro delivered versus 15 U Humalog
Studies Evaluating Development Formulations of LY900014 ‡			
I8B-FW-ITRJ (*ITRJ*)	Comparison of PK and GD of LY900014 formulations to Humalog.	Healthy subjects (24)	LY900014 formulations (15 mM or 25 mM citrate and either 1 µg/mL or 2 µg/mL treprostinil) versus 15 U Humalog.
I8B-FW-ITRE (*ITRE*)	Comparison of PK and GD of 3 insulin lispro doses of LY900014 to Humalog.	Healthy subjects (23)	LY900014 doses: 7.5 U; 15 U ; 30 U versus 15 U Humalog
I8B-JE-ITRK (*ITRK*)	Part A: Evaluation of safety and tolerability of treprostinil. Part B: Evaluation of PK of insulin lispro across a range of insulin lispro doses for a novel LY900014 formulation.	Healthy Japanese subjects (23)	Treprostinil alone: Part A (N=8): 1000 ng single bolus dose vs placebo LY900014: Part B (N=15): 7.5 U, 15 U, or 30 U of insulin lispro, vs 15 U Humalog
I8B-FW-ITRH (*ITRH*)	Part A: Effect of injection-to-mealtime on the PK and GD of LY900014 compared to Humalog following a single dose. Part B: PK and GD of LY900014 compared to Humalog following multiple doses.	T2D Patients (30)	LY900014 versus Humalog Part A: individualized doses at −15, 0, and +15 minutes relative to mealtime Part B: multiple daily dosing at time 0 relative to meal for 2 weeks
I8B-FW-ITRG (*ITRG*)	Part A: Effect of injection-to-mealtime on the PK and GD of LY900014 compared to Humalog following single dose. Part B: PK and GD of LY900014 compared to Humalog following multiple doses.	T1D Patients (30)	LY900014 versus Humalog Part A: individualized doses at −15, 0, and +15 minutes relative to mealtime Part B: multiple daily dosing at time 0 relative to meal for 2 weeks
I8B-MC-ITRP (*ITRP*)	8-hour euglycaemic clamp study to compare the PK and GD of insulin lispro in LY900014 Test (193 U/mL) versus insulin lispro in LY900014 Reference (95 U/mL)	Healthy subjects (24)	19-U dose of 193 U/mL versus 95 U/mL LY900014
I8B-FW-ITRF (*ITRF*)	4-period crossover MMTT study to evaluate PK and GD of LY900014 and Humalog	Patients with T1D using a pump (30)	Individualized SC dose of LY900014 and Humalog
LY900014 PK and GD Studies in Healthy Subjects – Euglycaemic Clamp			
I8B-MC-ITRL (*ITRL*)*	2-period crossover study evaluating PK and GD of LY900014 and Humalog during an 8-hour euglycaemic clamp	Healthy subjects (32)	15 U SC dose of LY900014 and Humalog
I8B-FW-ITSH (*ITSH*)*	6-period crossover study evaluating PK and GD of LY900014 and Humalog during a 10-hour euglycaemic clamp	Healthy subjects (42)	7, 15, and 30 U SC dose of LY900014 and Humalog
LY900014 PK and GD Studies in Patients with T1D and T2D – Euglycaemic Clamp			
I8B-MC-ITRR (*ITRR*)*	2-period crossover study evaluating PK and GD of LY900014 and Humalog during a 10-hour automated clamp	Young adult (41) and elderly (39) patients with T1D	15 U SC dose of LY900014 and Humalog
I8B-MC-ITRU (*ITRU*)*	2-period crossover study evaluating PK and GD LY900014 and Humalog during a 10-hour automated clamp	Patients with T2D (38)	15 U SC dose of LY900014 and Humalog
I8B-MC-ITRZ (*ITRZ*)*	2-period crossover study evaluating PK and GD of LY900014 and Humalog during a 10-hour automated clamp	Japanese patients with T1D (31)	15 U SC dose of LY900014 and Humalog
LY900014 PK and GD Studies in Patients with T1D and T2D – Meal Tolerance Test			
I8B-MC-ITRV (*ITRV*)*	4-period crossover MMTT study evaluating PK and GD of LY900014 and Humalog administered immediately before and 20	Patients with T1D (36)	Individualized SC dose of LY900014 and Humalog

Study	Description	Population (N)	Study Drug and Dose †
	minutes after the start of a test meal		
I8B-MC-ITRW (*ITRW*)*	4-period crossover MMTT study evaluating PK and GD of LY900014 and Humalog administered immediately before and 20 minutes after the start of a test meal	Patients with T2D (36)	Individualized SC dose of LY900014 and Humalog
LY900014 PK and GD Studies in Patients with T1D – Continuous SC Insulin Infusion			
I8B-MC-ITSC (*ITSC*)*	4-period crossover MMTT study to evaluate PK and GD of LY900014 and Humalog using different bolus delivery modes	Patients with T1D using a pump (24)	Individualized dose of LY900014 and Humalog
Bioavailability and bioequivalence studies			
I8B-MC-ITRT (*ITRT*)*	4-period crossover absolute and relative bioavailability study comparing the PK and GD of insulin lispro following LY900014 administered IV (single bolus injection) and SC into the abdomen, deltoid, or thigh during a 10-hour euglycaemic clamp	Healthy subjects (28)	15 U IV dose of LY900014 and 15 U SC dose of LY900014
I8B-MC-ITRQ (*ITRQ*)*$	4-period crossover bioequivalence study comparing the PK and GD of 200 units/mL and 100 units/mL formulations of LY900014 during a 10-hour euglycaemic clamp	Healthy subjects (49)	15 U SC 100 U/mL LY900014 15 U SC 200 U/mL LY900014
I8B-MC-ITSS (*ITSS*)*	4-period crossover bioequivalence study comparing the PK and GD of 200 units/mL and 100 units/mL formulations of LY900014 during a 10-hour euglycaemic clamp	Healthy subjects (68)	15 U SC 100 U/mL LY900014 15 U SC 200 U/mL LY900014
Humalog studies			
F3Z-MC-IOEK (IOEK)	Comparative study to evaluate the PK and GD of different insulin therapies in patients with impaired hepatic function	Patients with T2D (22)	Humalog and Humulin I vs Humulin R and Humulin I
F3Z-MC-IOEI (IOEI)	Primary objective: Crossover study to compare the PK and GD of Humalog and Humulin R in patients with impaired renal function Secondary objective: Examine the effects of Humalog on serum potassium concentrations and QTc intervals compared to Humulin R	Patients with T2D (25)	0.3 U/kg Humalog and Humulin R
F3Z-MC-IOEY (IOEY)	Crossover study to evaluate the efficacy of IV infused Humalog compared to IV infused Humulin R	Patients with T1D (21)	Individualized IV infused Humalog and Humulin R

GD = glucodynamics; **IV** = intravenous; **MMTT** = mixed meal tolerance test; **PK** = pharmacokinetics; **SC** = subcutaneous; **T1D** = type 1 diabetes; **T2D** = type 2 diabetes; **U** = units.
† all doses administered subcutaneously unless otherwise noted
‡ all studies included formulations of insulin lispro 100 units/mL with 1 ug/mL treprostinil and 15 mM citrate (consistent with the commercial formulation of LY900014 100 units/mL) but did not use commercial manufacturing processes and may have included other excipients not included in the final commercial formulation.
*****Study conducted using final commercial formulation of LY900014.
$ In Study ITRQ, the insulin pens containing 200 units/mL LY900014 were inadequately primed, resulting in lower doses being administered. The study was repeated as the pivotal bioequivalence study I8B-MC-ITSS.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

LY900014 is a new formulation of insulin lispro that utilizes two enabling excipients - treprostinil and sodium citrate - with independent mechanisms to accelerate the absorption of insulin lispro from the site of injection. A microdose of treprostinil, a prostacyclin analogue approved for treatment of pulmonary arterial hypertension (PAH), induces local vasodilation to enhance the absorption of insulin lispro. The addition of citrate in LY900014 enhances the local vascular permeability to speed insulin absorption. The active pharmaceutical ingredient, insulin lispro, is identical in LY900014 and Humalog. Therefore, once systemically absorbed, the disposition pharmacokinetics and drug interaction potential are assumed to be similar between LY900014 and Humalog.

LY900014 is intended for subcutaneous (SC) use and for intravenous (IV) use to improve glycaemic control in patients with type 1 diabetes mellitus (T1D) or type 2 diabetes mellitus (T2D). LY900014 is available in 2 dosage strengths: 100 units/mL and 200 units/mL.

The clinical pharmacology studies evaluated LY900014 following different routes of administration, including SC and IV injections and continuous subcutaneous insulin infusion (CSII). Comparisons were made to Humalog throughout the development. Of the 22 clinical pharmacology studies performed, 1 study evaluated sodium citrate, 3 studies evaluated treprostinil, 7 studies were conducted with development formulations of LY900014, and 11 studies were conducted with the final commercial formulation (Table 3). No bioequivalence study was performed between the development formulations and the final commercial LY900014 formulation since the latter one was used in all of the Phase 3 studies and in the clinical pharmacology studies that support product labelling. The final commercial formulation was used in all clinical studies presented in this report.

Bioanalytical methods

The Applicant used the following analytical methods: 1. a liquid chromatographic-mass spectrometry/mass spectrometry (LC-MS/MS) to analyse the amount of treprostinil in human plasma samples, 2. to measure free LY275585 in human serum, three different assays were used; i) radioimmunoassay (RIA) was used in one clinical study, ii) in three subsequent studies an ELISA was performed, and iii) in all other instances, another ELISA assay with two subsequent iterations was used, and 3. for detection and characterisation of anti-drug antibodies to LY275585, a radioligand binding assay (RBA) was performed.

To analyse the amount of treprostinil a LC-MS/MS was performed. A sufficient description of the method and the method validation have been provided. Compliance of the assay with respect to accuracy and precision, determination of matrix effects, range, selectivity, and stability are shown. In addition, carryover and reproducibility of the reinjections were analysed. Appropriate calibration curve for the acceptance criteria are set. Calibration curve standards (STD) are prepared separately from the quality control (QC) samples. Robustness of the analytical method was not evaluated. The Applicant uses treprostinil-13C2D as an internal standard (IS) for the assay. Stability for two years is stated. For each clinical trial, the method qualification runs were performed prior to the studies. The method performance of the assay in the study met the defined criteria. The required criteria were met and the reproducibility of the bioanalytical method is therefore shown.

The amount of LY275585 in human serum was determined with two different methods: radioimmunoassay (RIA) and two different ELISAs. Sufficient validation data from the RIA method was included. The method is validated between 0.2 to 30 ng/mL. Precision and accuracy, dilution linearity, and method selectivity as well as stability (freeze-thaw, RT, +2-8°, and long term) were assessed. The method's selectivity was amended to include method sensitivity. System suitability criteria for calibration

curve were set. In addition, acceptance criteria for quality control are provided. Quantization of LY275585 in the samples was achieved by interpolation from the standard calibration curve. Some minor issues with the method validation was observed e.g. information about the positive control and matrix is missing and robustness of the method was not evaluated. However, since the clinical trial ITAO was performed in the earlier stages of the drug development and no pivotal data to support the MAA is collected in this trial, no further information is requested.

For ELISA 3400139, a sufficient description of the method including all the method validation have been provided. Validation of the method in human serum included: selectivity, dilution linearity, evaluation of the prozone effect, working calibration range, inter and intra-assay precision and accuracy (including LLOQ and ULOQ assessments). In addition, the stability of validation samples was assessed. Validation data also demonstrated that hemolysis of up to 5% has no impact on the assay. For each clinical trial (F3Z-FW-ITCA, I8B-FW-ITRA, and I8B-FW-ITRE), the method qualification runs were performed prior to the studies. The method performance of the assay in the study met the defined criteria. In general, it can be agreed that the method is appropriately validated, however, specificity was not evaluated as required in the bioanalytical method validation guideline. According to the Applicant, the quantification of LY275585 was not affected by the presence of human insulin (10 ng/mL). Specificity was evaluated in lipemic serum, haemolysed serum, and human serum with endogenous insulin.

Sufficient description of the ELISA methods 3400449, 3400620, and 3400690 including all the method validation have been provided and is considered acceptable. Validation of the method in human serum included: selectivity, dilution linearity, evaluation of the prozone effect, working calibration range, inter and intra-assay precision and accuracy (including LLOQ and ULOQ assessments). In addition, the stability of validation samples was assessed. Method 3400449 was used in seven clinical trials (ITRK, ITRF, ITRL, ITSC, ITRJ, ITRG, and ITRP). Method 3400620 was used in trial ITRH, and method 3400690 in trials ITSH, ITRU, ITRR, ITRT, ITRQ, ITRV, ITRW, ITRZ, and ITSS. Method qualification runs were performed prior to the studies. Method performance of the assays in the study met the defined criteria. In addition, the Applicant has provided acceptable cross-validation studies for RIA and ELISA 3400139 as well as for ELISA 3400139 and ELISA 3400690.

Some general consideration is made for all validated ELISAs for detection of insulin in human serum. Acceptance criteria for accuracy and precision are higher (the mean back-calculated concentrations had to be within ± 20% relative error (± 25% relative error at the LLOQ and ULOQ) than stated in the bioanalytical method validation guideline for non-ligand binding assays where ± 15% and ± 20% REs are recommended for the mean concentrations and LLOQ/ULOQ, respectively. However, as for all the methods, the validation results are considered appropriate; the proposed acceptance criteria can be accepted. As part of the D181 responses, the Applicant has provided satisfactory evidence on the robustness of the bioanalytical methods.

For quantification of anti-drug antibodies, a semi-quantitative method is used, thus the results are not presented as ADA titers. Patient samples are considered as ADA positive when the assay result (Δ%B/T value) is over the assay cut point. As described by the Applicant the Δ%B/T value is a difference between %B/T radioactivity measurements of set A and set B samples. Set A contains the diluted sample extract in the buffer while set B contains excess LY275585 competing with the bound radiolabeled tracker. Due to the excess LY275585 competition the radioactivity is reduced and thus the binding is confirmed. Evaluation of immunogenicity was based on data from three Phase 3 and 10 clinical pharmacology studies.

The Applicant will use a 2-tiered approach to detect and characterize anti-insulin lispro antibodies in serum samples from clinical trials. The clinical study samples were assessed in Tier 1 (screening) for the presence of ADA against insulin lispro. If a serum sample assessed in Tier 1 is found to produce a sign greater than or equal to the Tier 1 assay cut point, it is evaluated in Tier 2, which assesses whether the

anti-insulin lispro antibodies are cross-reactive to native insulin (competition with excess unlabeled native insulin instead of excess unlabeled insulin lispro). In general, the Applicant has shown a compliance of the assay with respect to minimal required dilution (MRD), specificity and assay cut points, precision, sensitivity, drug and insulin tolerance, determination of matrix effects, stability and robustness. Validation acceptance criteria for intra and inter assay precision (± 25% CV) and for matrix effect (± 30%) are higher than stated in the EMA bioanalytical method validation guideline, however, based on the provided validation data, the limits can be accepted. Guinea pig anti-insulin antibody serum was used as a positive control and the antibody was appropriately characterised.

Absorption

Study ITRT was an absolute and relative bioavailability study conducted as an open-label, randomized, 4-period crossover, 10-hour euglycaemic clamp study in healthy subjects to compare the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) profiles following a 15 units (U) dose of LY900014 administered IV and SC into the thigh, deltoid, or abdomen. One subject in study ITRT had extremely low insulin lispro exposure following IV administration of LY900014, possibly due to incomplete drug administration and/or incomplete flushing of the cannula. The subject was excluded from PK analyses, which was considered to be acceptable.

Absolute bioavailability of insulin lispro was approximately 65% following SC injection of LY900014 at each site. The insulin lispro concentration-versus-time profiles following SC injection into the abdomen and deltoid were superimposable, whereas the Cmax was lower and the concentration vs time curve was broader following injection into the thigh in comparison to both the abdomen and deltoid (Figure 3). To justify injection into the thigh, the Applicant performed indirect comparison of the PK parameters obtained after SC injection of LY900014 in the abdomen, deltoid and thigh (study ITRT) with those obtained after SC injection of Humalog in the abdomen (studies ITSH and ITRL). Although early exposure was lower after injection of LY900014 in the thigh compared to other injection sites, absorption was still significantly accelerated compared to Humalog (Figure 4). The results of relative bioavailability comparison are summarised in Table 4.

Figure 3. Arithmetic mean (±SE) serum concentration-versus-time (left) and the first 30 minutes (right) for single 15 U SC injections of LY900014 into the abdomen, deltoid, and thigh of healthy subjects (Study ITRT)

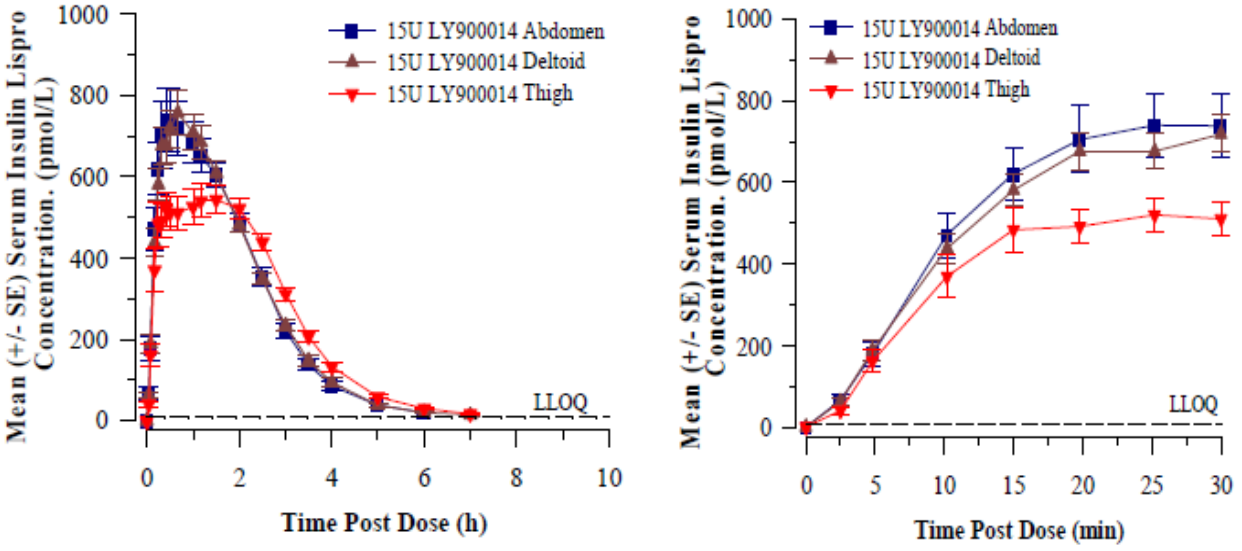
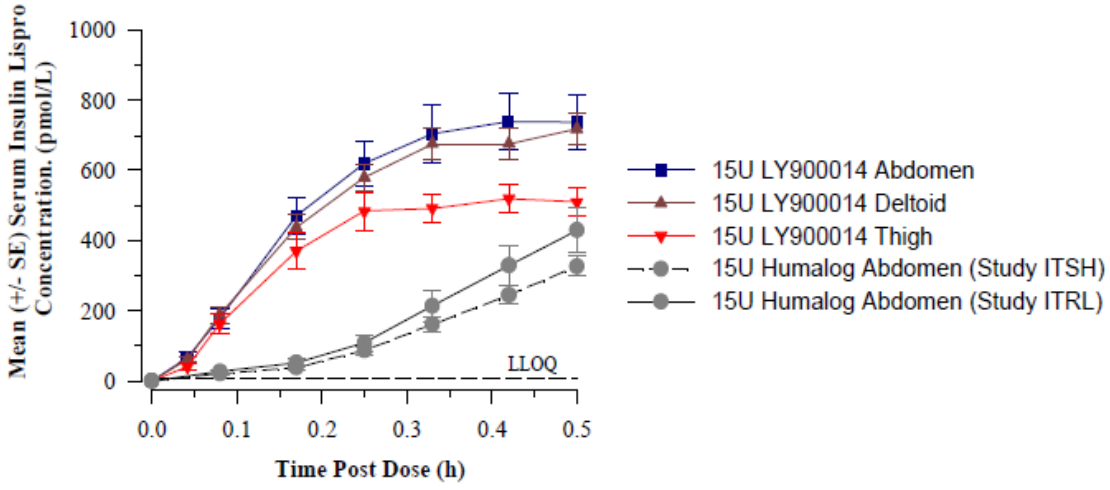


Figure 4. Arithmetic mean (±SE) serum concentration-versus-time profiles for single SC injections of 15 LY900014 into the abdomen, deltoid, or thigh (Study ITRT) and single SC injection of 15U Humalog into the abdomen (Studies ITRL and ITSH) of healthy subjects within first 30 minutes postdose.



Abbreviations: LLOQ = lower limit of quantification; SC = subcutaneous; SE = standard error.
LLOQ is 8.61 pmol/L.

Table 4. Relative Bioavailability Comparison between SC Injection Sites Deltoid vs Abdomen and Thigh vs Abdomen. (Completers, N=25) (Study ITRT)

Parameter (unit)	Ratio of Least Squares Geometric Means (90% Confidence Interval)	
	Deltoid/Abdominal Wall	**Thigh/Abdominal Wall**
AUC(0-∞) (pmol·h/L)	1.03 (0.993, 1.08)	1.00 (0.962, 1.04)
C_{max} (pmol/L)	1.05 (0.928, 1.19)	0.832 (0.736, 0.940)

AUC(0-∞) = AUC from zero to infinity; **C_{max}** = maximum observed drug concentration.

Bioequivalence

The first bioequivalence study, ITRQ, failed due to inadequately priming of the LY900014 U-200 insulin pens. However, bioequivalence between U-100 and U-200 formulation was shown in the repeat bioequivalence study ITSS.

Comparable pharmacokinetics for the concentrated form (200 units/mL) of LY900014 relative to LY900014 100 units/mL following SC administration was demonstrated in a 2-sequence, 4-period, randomized, replicated-crossover study in healthy subjects (study ITSS). Statistical analysis for the pre-defined primary PK parameters $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}\infty)}$, and Cmax demonstrated comparable pharmacokinetics for the 200 units/mL and the 100 units/mL formulations (Table 5). Partial AUCs for secondary PK parameters reflecting early insulin lispro exposure [AUC(0-15min) and AUC(0-30min)] were slightly lower for the U-200 formulation, but within the conventional limits (0.80, 1.25) of bioequivalence. The ratio (90% CI) of U-200/U-100 were 0.882 (0.836, 0.931) and 0.863 (0.828, 0.900) for AUC[0-15min] and AUC[0-30min], respectively, for subjects who completed all periods.

Table 5. Primary PK Parameters of Insulin Lispro after SC Administration of 15 U of 100 U/mL LY900014 and 200 U/mL LY900014 Formulations (Study ITSS)

Parameter	Treatment	Geometric LSM	Ratio of Geometric LSM 200 U/mL:100 U/mL	90% CI for the ratio
All evaluable data (N=68; n=133) [a]				
AUC(0-t_{last}) (pmol.h/L)	100 U/mL LY900014	1673	**1.01**	**(0.960, 1.06)**
	200 U/mL LY900014	1689		
AUC(0-∞) (pmol.h/L)	100 U/mL LY900014	1688	**1.01**	**(0.961, 1.06)**
	200 U/mL LY900014	1704		
C_{max} (pmol/L)	100 U/mL LY900014	678	**0.971**	**(0.881, 1.07)**
	200 U/mL LY900014	659		
Completers (N=65; n=130) [b]				
AUC(0-t_{last}) (pmol.h/L)	100 U/mL LY900014	1659	**1.01**	**(0.997, 1.03)**
	200 U/mL LY900014	1684		
AUC(0-∞) (pmol.h/L)	100 U/mL LY900014	1674	**1.01**	**(0.997, 1.03)**
	200 U/mL LY900014	1699		
C_{max} (pmol/L)	100 U/mL LY900014	675	**0.975**	**(0.933, 1.02)**
	200 U/mL LY900014	658		

AUC(0-t_{last}) =AUC from time zero to the last time point with a measurable concentration; **AUC(0-∞)** = AUC from time zero to infinity; **C_{max}** = maximum observed concentration; **LSM** = least squares mean; **N** = Number of subjects; **n** = number of observations.

[a] Model: Log(PK) = Period + Treatment + Sequence + Subject + Random Error, where Subject is fitted as a random effect and a repeated statement is used

[b] Model: Log(PK) = Period + Treatment + Sequence + Subject(Sequence) + Random Error

Distribution

Geometric mean (range) of volume of distribution (Vz) following IV injection of a 15 U dose of LY900014 was 34 L (16 to 53 L), calculated using conventional non-compartmental analysis.

Elimination

Geometric mean (range) of clearance following IV injection of a 15 U dose of LY900014 was 32.3 L/h (23.3 to 49.5 L/h), calculated using conventional non-compartmental analysis.

Dose proportionality and time dependencies

Study ITSH was a randomised, subject- and investigator-blind, 6-period complete crossover study in healthy subjects to evaluate the PK and glucodynamic characteristics of LY900014 compared to Humalog across a range of doses (single SC doses of 7, 15, and 30 U).

The insulin lispro concentration time profile increased with LY900014 dose as shown in the Figure below. The resulting insulin lispro exposure (AUC[0-∞] and Cmax) following administration of LY900014 shows an increase by dose.

The degree of dose proportionality for insulin lispro was assessed by fitting the power model to AUC[0-10h], AUC[0-∞] and C_{max} versus dose for each dose level of LY900014. When dose proportionality exists, the exponent on dose in the equation should be close to 1. The exponents for the insulin lispro C_{max}, AUC(0-10h), and AUC(0-∞) across the dose range of 7 to 30 U were 0.959 (95% CI: 0.910 to 1.01), 1.08 (95% CI: 1.05 to 1.10), and 1.08 (95% CI: 1.05 to 1.10), respectively. The ratios of dose-normalised geometric LS means for the insulin lispro C_{max}, AUC(0-10h), and AUC(0-∞) across the dose range of 7 to 30 U were 0.942 (95% CI: 0.877 to 1.01), 1.12 (95% CI: 1.08 to 1.16), and 1.12 (95% CI: 1.08 to 1.16), respectively. This indicated that increase in Cmax was dose proportional and increases in AUC(0-10h) and AUC(0-∞) were approximately dose proportional.

Figure 5. Arithmetic mean (±SE) of serum insulin lispro concentration vs time profiles following the administration of 7, 15, and 30 U of LY900014 (Study ITSH).

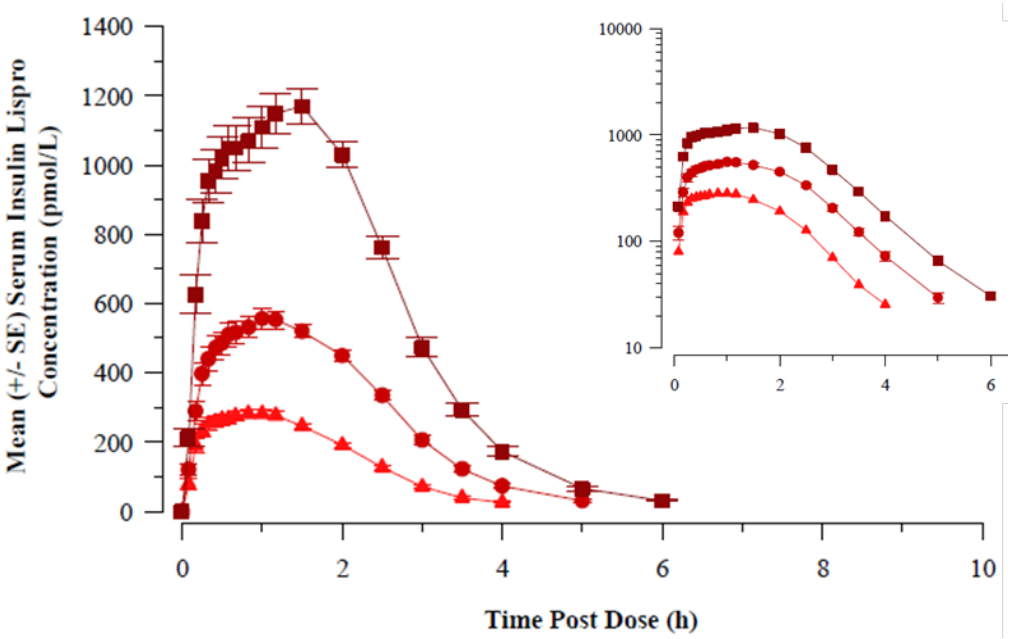
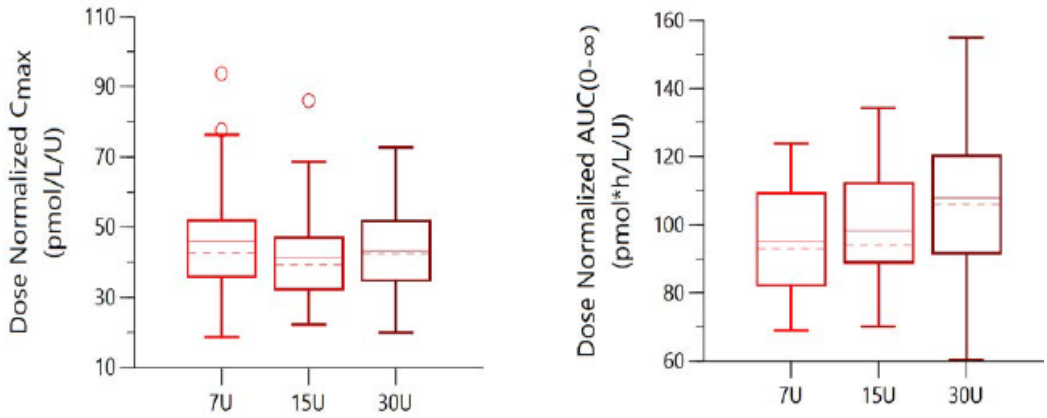


Figure 6. Box plot of dose-normalised insulin lispro Cmax and AUC(0-∞) vs dose following administration of 7, 15, or 30 U of LY900014 SC injection (Study ITSH).



Boxplot dashed lines represent the medians; solid lines represent the means. The bottom and top of the boxes represent the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 of the interquartile range of the lower quartile and the highest value still within 1.5 of the interquartile range of the upper quartile.

Variability

Intra- and inter-individual variability for C_{max} and AUC(0-∞) observed in patients with T1D, T2D, and in healthy subjects in representative 4-period cross-over studies ITRV, ITRW and ITSS is summarised in Table 6 through Table 7. Note that the dose was individualised in studies ITRV and ITRW, which increases the inter-individual variability of C_{max} and AUC.

Results of the population PK analysis indicated that inter-individual variability is small (6.2 to 24.6%) for disposition parameters following IV injection, moderate (31.4%) for bioavailability, and large (42.2 to 78.7%) for absorption rate parameters following SC injection.

Table 6. Variability Analysis of the PK Parameters of Insulin Lispro after SC Administration of LY900014 Compared to Humalog in Adult Patients with T1D (Study ITRV)

Patients with Evaluable Data for Both Treatment Periods				
	Intra-individual CV% (95% CI)		**Inter-individual CV% (95% CI)**	
	LY900014	Humalog	LY900014	Humalog
Cmax (pmol/L)	26.6 (21.1, 36.2)	21.0 (16.7, 28.6)	44.3 (33.6, 65.8)	47.8 (36.9, 68.7)
AUC(0-∞) (pmol.h/L)	24.1 (19.3, 32.2)	10.2 (8.15, 13.6)	55.3 (42.4, 80.7)	56.9 (44.4, 80.2)
Patients with Evaluable Data for Both Treatment Periods Excluding One Outlier (Patient 9206)				
	Intra-individual CV% (95% CI)		**Inter-individual CV% (95% CI)**	
	LY900014	Humalog	LY900014	Humalog
Cmax (pmol/L)	18.4 (14.6, 24.9)	20.1 (16.0, 27.3)	46.8 (36.1, 66.9)	48.8 (37.6, 70.4)
AUC(0-∞) (pmol.h/L)	12.9 (10.3, 17.2)	9.97 (7.96, 13.3)	56.1 (43.6, 79.9)	57.9 (45.0, 82.2)
Model: Log(PK) = Period + Treatment + Patient + Random Error, where Patient is fitted as a random effect and a repeated statement is used				

Table 7. Variability Analysis of the PK Parameters of Insulin Lispro after SC Administration of LY900014 Compared to Humalog in Adult Patients with T2D (Study ITRW)

	Intra-individual CV% (95% CI)		**Inter-individual CV% (95% CI)**	
	LY900014	Humalog	LY900014	Humalog
Cmax (pmol/L)	23.4 (18.8, 31.0)	19.3 (15.5, 25.5)	57.9 (44.8, 83.3)	63.7 (49.4, 91.1)
AUC(0-∞) (pmol.h/L)	13.2 (10.6, 17.5)	15.3 (12.3, 20.3)	61.5 (48.0, 86.6)	66.8 (51.9, 95.3)
Model: Log(PK) = Period + Treatment + Patient + Random Error, where Patient is fitted as a random effect and a repeated statement is used				

Table 8. Variability Analysis of the PK Parameters of Insulin Lispro after SC Administration of LY900014 100 U/mL and 200 U/mL Formulations in healthy subjects (Study ITSS)

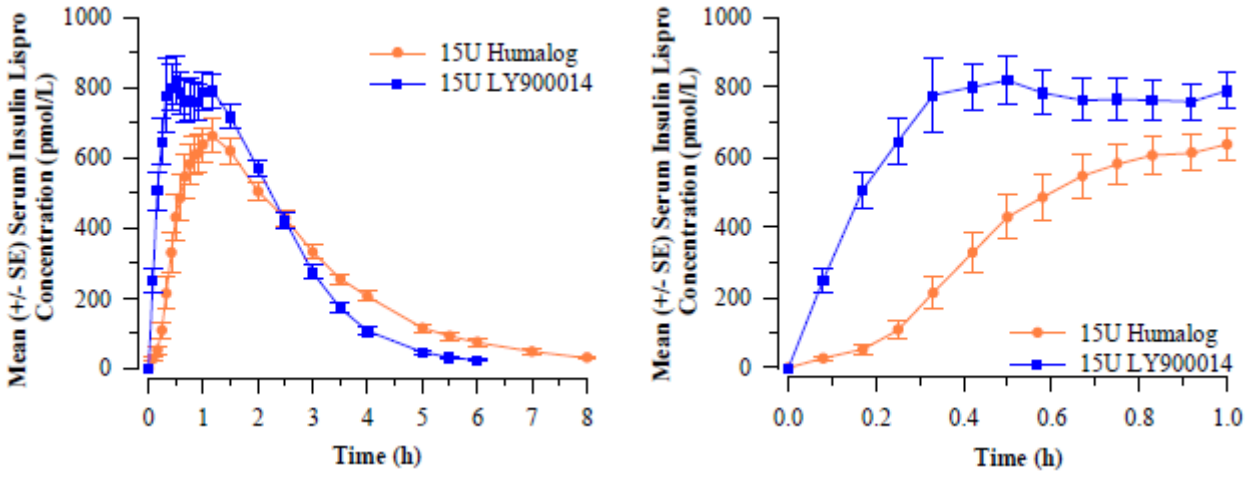
	Intra-individual CV% (90% CI)		**Inter-individual CV% (90% CI)**	
	LY900014 100 U/mL	LY900014 200 U/mL	LY900014 100 U/mL	LY900014 200 U/mL
Cmax (pmol/L)	16.3 (14.3, 19.2)	25.4 (22.2, 29.9)	32.7 (28.0, 39.6)	30.4 (25.3, 38.7)
AUC(0-∞) (pmol.h/L)	9.51 (8.30, 11.2)	8.30 (7.25, 9.74)	16.5 (14.1, 20.0)	16.1 (13.8, 19.3)
Model: Log(PK) = Period + Treatment + Sequence + Subject + Random Error, where Subject is fitted as a random effect and a repeated statement is used				

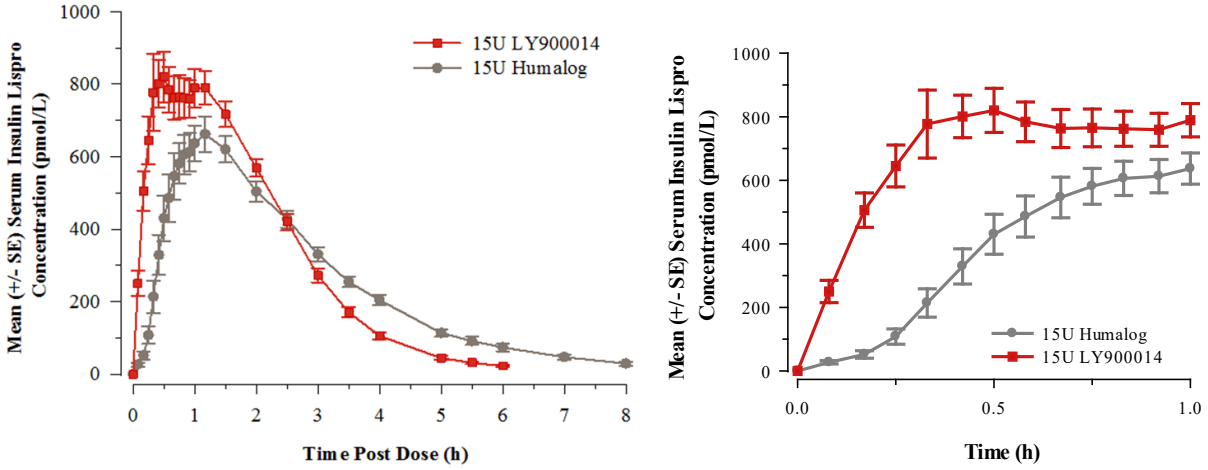
Pharmacokinetics of LY900014 vs Humalog: SC injection

Study ITRL was a randomized, subject- and investigator-blind, 2-treatment, 2-period, crossover study in healthy subjects. It compared the PK and GD of insulin lispro following a single 15 U SC dose of LY900014 with the PK and GD of a single 15 U SC dose of Humalog.

The mean insulin lispro exposure following administration of single 15 U doses of LY900014 and insulin lispro (Humalog) is presented in the Figure below. LY900014 showed a faster, earlier insulin lispro absorption compared to Humalog as indicated by left shifting of the concentration-time curve and statistically significant ($p<0.0001$) changes in the early 50% t_{max}, AUC(0-15min), AUC(0-30min), and AUC(0-1h). Similarly, the late insulin lispro exposure [AUC(2-8h)] was reduced with LY900014 compared to Humalog ($p<0.0001$). This faster absorption of insulin lispro resulted in 1.28-fold higher C_{max} following LY900014 compared to Humalog ($p<0.0001$). However, the overall insulin exposure [AUC(0-∞)] was not significantly different between LY900014 and Humalog (ratio of geometric LSM 1.03; 90% CI 0.99-1.08).

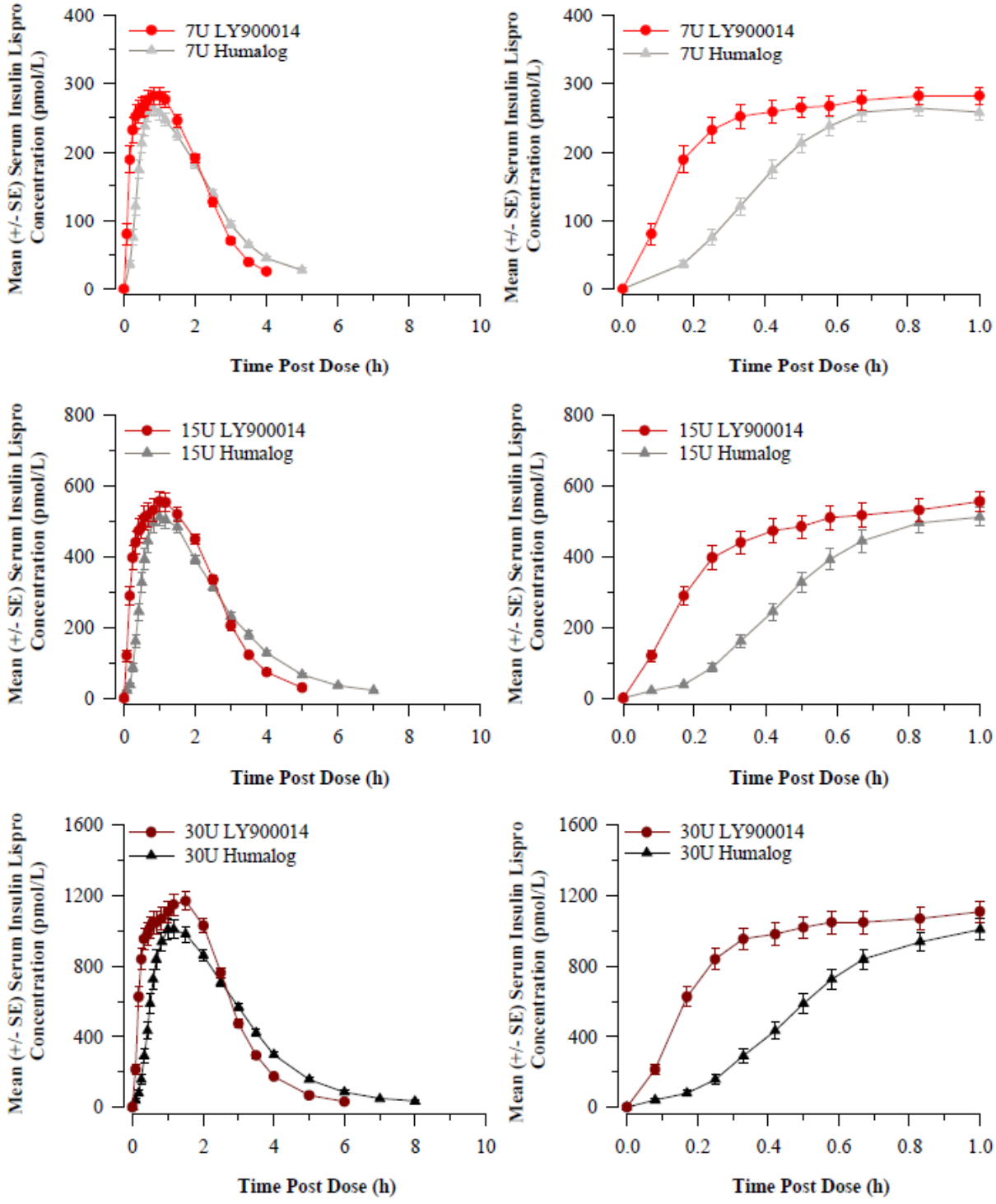
Figure 7. Mean (±SE) insulin lispro concentration vs time for the duration of the clamp (left) and for the first hour (right) by treatment following 15 U doses of LY900014 and Humalog. (Study ITRL)





In study ITSH in healthy subjects, LY900014 showed an accelerated lispro absorption compared with Humalog, seen as left shifting of the concentration-time curve at each dose level (Figure 8). Statistically significant difference between LY900014 and Humalog was shown for early exposure PK parameters onset of appearance, early 50% t_{max}, AUC(0-15min), AUC(0-30min), and AUC(0-1h) ($p<0.0001$ for each parameter at each dose level). A reduction in late insulin exposure and a shorter exposure duration compared to Humalog was also shown across all 3 dose levels. The tmax or overall insulin exposure (AUC[0-∞]) was not significantly different between LY900014 and Humalog, but the average C_{max} was 12% to 19% higher following LY900014 injection ($p<0.0001$ to $p=0.0026$).

Figure 8. Mean (±SE) insulin lispro concentration vs time (left) and the first hour (right) following 7 (top), 15 (middle), and 30 U (bottom) dose of either LY900014 or Humalog (Study ITSH).

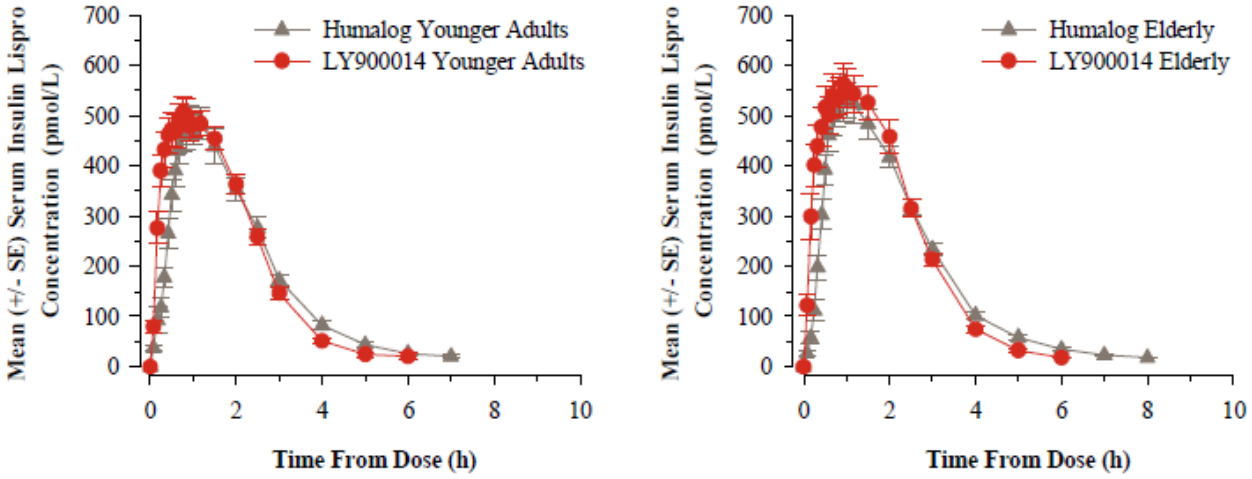


Study ITRR was a randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study in patients with T1D. The primary objective was to evaluate the PK of insulin lispro following administration of a single 15 units SC dose of LY900014 compared to Humalog in elderly patients (≥65 years) and younger adults (18 to 45 years).

The mean insulin lispro exposure following administration of single 15 U doses of LY900014 and Humalog is presented in Figure 9. LY900014 showed an accelerated lispro absorption compared to Humalog as

indicated by left shifting of the concentration-time curve and statistically significant (p<0.0001 to p=0.0002) changes in the AUC(0-15min), AUC(0-30min), AUC(0-1h), onset of appearance, and early 50% t_{max} values in young adult patients as well as in elderly patients. Similarly, the late insulin lispro exposure was reduced and the exposure duration was shorter with LY900014 compared to Humalog. However, the overall insulin exposure AUC(0-∞), t_{max}, or C_{max} was not significantly different between LY900014 and Humalog.

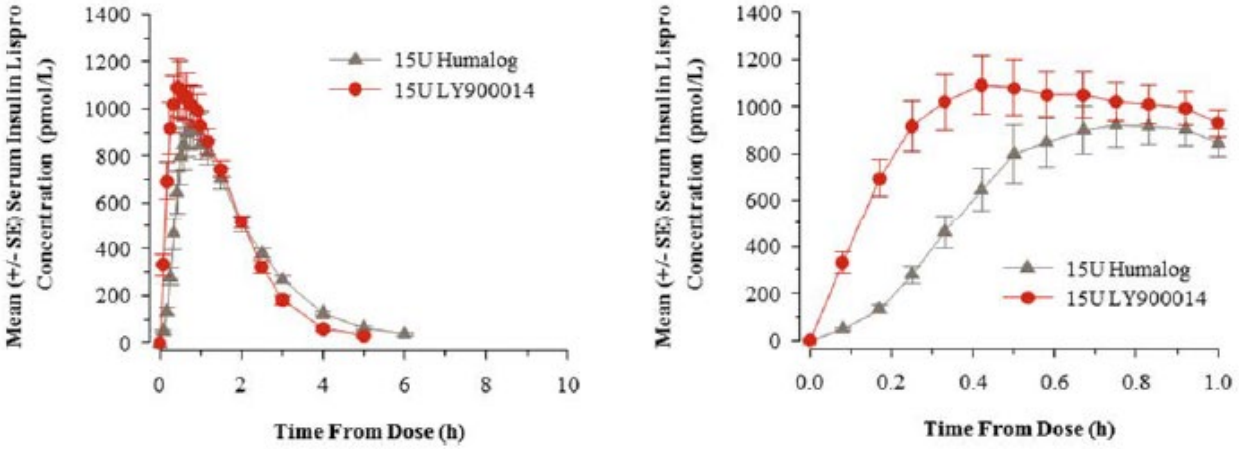
Figure 9. Mean insulin lispro concentration (±SE) versus time following administration of 15 U Humalog and LY900014 in younger adults (left) and elderly (right) patients with T1D



Study ITRZ was a randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study in Japanese patients with T1D. The primary objective of this study was to compare the PK of insulin lispro following administration of a single 15 U SC dose of LY900014 and Humalog in Japanese patients with T1D.

The mean insulin lispro exposures following administration of single 15 U doses of LY900014 and Humalog are presented in Figure 10. LY900014 showed an accelerated lispro absorption compared to Humalog, as indicated by left shifting of the concentration-time curve and statistically significant (p<0.0001 to p=0.0013) changes in the early 50% t_{max}, AUC(0-15min) ,AUC(0-30min), AUC(0-1h). Similarly, the late insulin lispro exposure was reduced and the exposure duration was shorter with LY900014 compared to Humalog. However, the overall insulin exposure AUC(0-∞) and Cmax was not significantly different between LY900014 and Humalog. The C_{max} of insulin lispro was 1.16-fold higher with LY900014 compared to Humalog (p=0.0587).

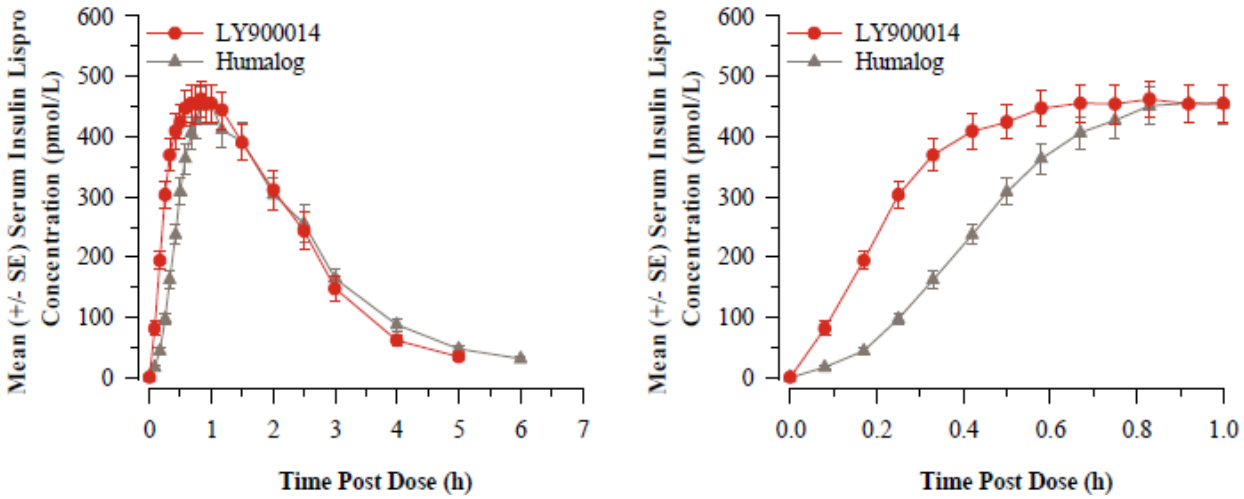
Figure 10. Mean insulin lispro concentration (±SE) vs time for the duration of the study (left) and for the first hour (right) by treatment following 15 U dose of LY900014 and 15 U dose of Humalog in Japanese patients with T1D (Study ITRZ).



Study ITRV was a patient- and investigator-blind, randomized, 2-treatment, 4-period crossover study in patients with T1D. The primary objective was to evaluate the PK of insulin lispro following a single SC injection of LY900014 and Humalog. The insulin dose was individualized by patient for investigation of the pharmacodynamic objectives of the study and was maintained over the study periods for each treatment. The average dose was 12.4 U (0.155 U/kg) for the dose range of 6 to 34 U (0.0764 to 0.38 U/kg).

Figure 11 presents the mean insulin lispro exposures over time and for the first hour after administration of LY900014 and Humalog. LY900014 showed an accelerated insulin lispro absorption compared to Humalog, as indicated by left shifting of the concentration-time curve and statistically significant ($p<0.0001$) changes in the PK parameters onset of appearance, early 50% t_{max}, AUC(0-15min), AUC(0-30min) and AUC(0-1h). Additionally, the late insulin lispro exposure was reduced and the exposure duration was shorter with LY900014 compared to Humalog. The overall insulin exposure parameters AUC(0-∞), t_{max}, or C_{max} were not significantly different between LY900014 and Humalog ($p=0.0615$ to $p=0.4195$).

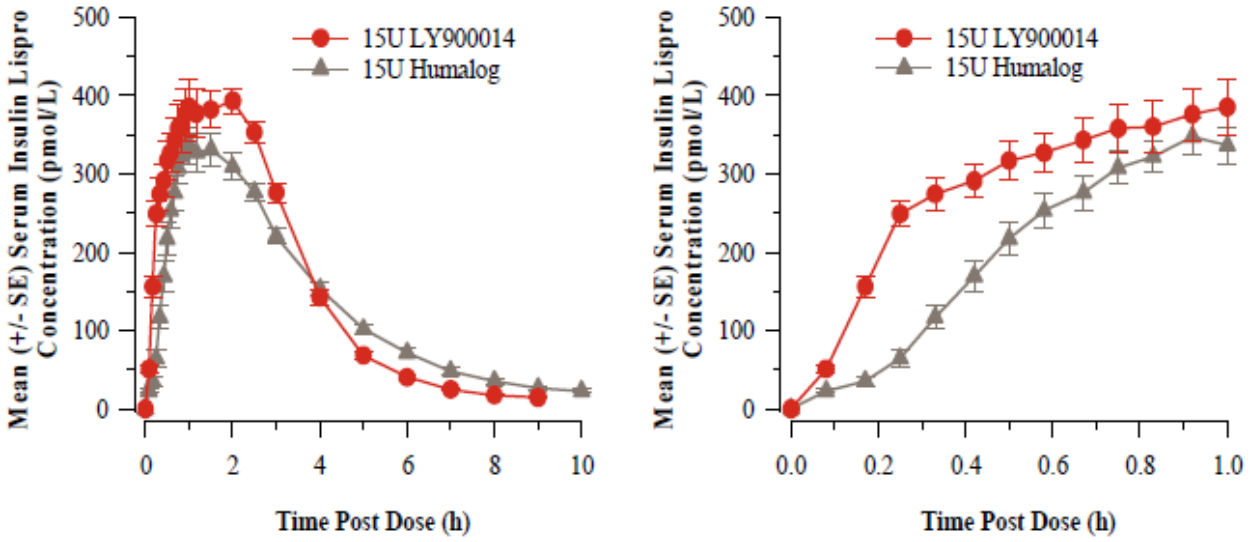
Figure 11. Mean insulin lispro concentration (±SE) vs time (left) and the first hour (right) by treatment following administration of LY900014 and Humalog (Study ITRV).



Study ITRU was a randomized, patient- and investigator-blind, 2-treatment, single-dose, 2-period, 10-hour glycaemic clamp, crossover study. The primary objective was to evaluate the PK of insulin lispro following administration of a single 15 U SC dose of LY900014 compared to Humalog in patients with T2D.

Figure 12 presents the mean insulin lispro exposures over time and for the first hour after administration of LY900014 and Humalog. LY900014 showed an accelerated insulin lispro absorption compared to Humalog, as indicated by left shifting of the concentration-time curve and statistically significant ($p<0.0001$) changes in the PK parameters onset of appearance, early 50% t_{max}, AUC(0-15min), AUC(0-30min) and AUC(0-1h). The C_{max} was 19% higher (95% CI 9% to 31%), and the late insulin lispro exposure was reduced with LY900014 compared to Humalog. Additionally, the duration of exposure was shorter with LY900014 compared to Humalog. The overall insulin exposure AUC(0-∞) and t_{max} were not significantly different between LY900014 and Humalog ($p=0.0676$ and $p=0.1002$, respectively).

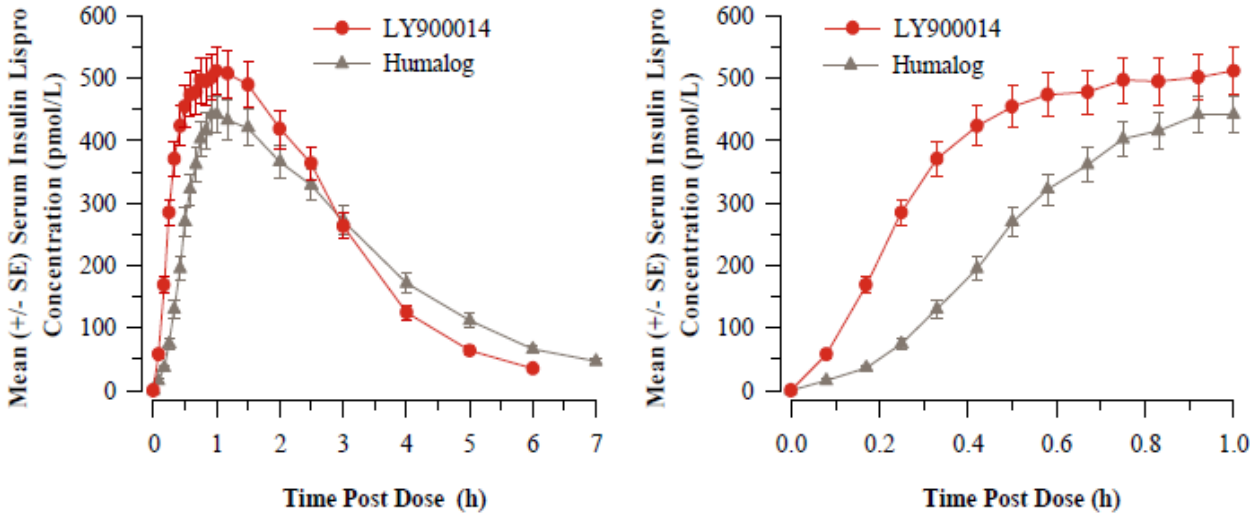
Figure 12. Mean insulin lispro concentration (±SE) versus time (left) and the first hour (right) by treatment following 15-U dose of LY900014 and 15-U dose of Humalog (Study ITRU).



Study ITRW was a patient- and investigator-blind, randomized, 2-treatment, 4-period crossover study in patients with T2D. The primary objective was to evaluate the PK of insulin lispro following a single SC injection of LY900014 and Humalog in patients with T2D. The insulin dose was individualized by patient for investigation of the pharmacodynamic objectives of the study and was maintained over the study periods for each treatment. The average dose was 14.3 U (0.15 U/kg) for the dose range of 5 to 40 U (0.0587 to 0.365 U/kg) of LY900014 and Humalog.

The mean insulin lispro exposure following administration of LY900014 and Humalog is presented in Figure 13. LY900014 showed an accelerated insulin lispro absorption compared to Humalog, as indicated by left shifting of the concentration-time curve and statistically significant ($p<0.0001$) changes in the PK parameters onset of appearance, early 50% t_{max}, AUC(0-15min), AUC(0-30min) and AUC(0-1h). The C_{max} was 15% higher (95% CI 7% to 23%), and the late insulin lispro exposure was reduced with LY900014 compared to Humalog. The overall insulin exposure AUC(0-∞), or t_{max}, was not significantly different between LY900014 and Humalog.

Figure 13. Mean insulin lispro concentration (±SE) vs time (left) and the first hour (right) by treatment following administration of LY900014 and Humalog (Study ITRW).



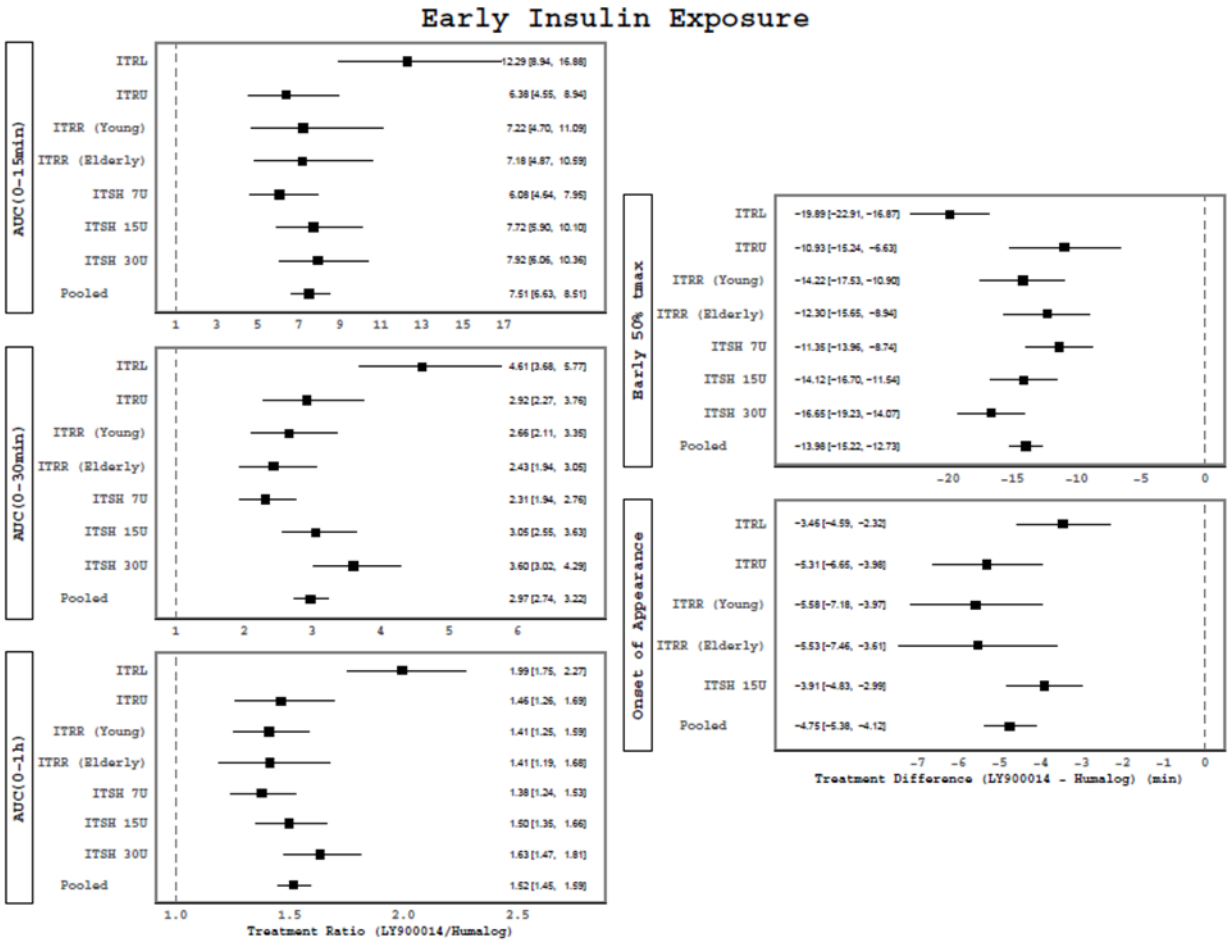
Meta-analysis of pharmacokinetics: LY900014 vs Humalog

The Applicant conducted a meta-analysis to summarize the pharmacokinetics after SC injection of a single dose of either a 7, 15 or 30 units (U) LY900014 compared to Humalog. Studies included in the PK meta-analysis (ITRL, ITRU, ITRR, ITSH) used the final commercial formulation of LY900014, included Humalog as the comparator, collected PK data in a cross over study design, used similar timing for PK collection, and conducted comparisons between LY900014 and Humalog using the same dose level.

Forest plots presented below include the individual study 95% CIs using the analysis models used in the studies. The primary protocol-specified PK endpoints in studies ITRL, ITRU, ITRR and ITSH were AUC(0-30min) and time to half maximal drug concentration (early 50% t_{max}), which reflect the early insulin exposure.

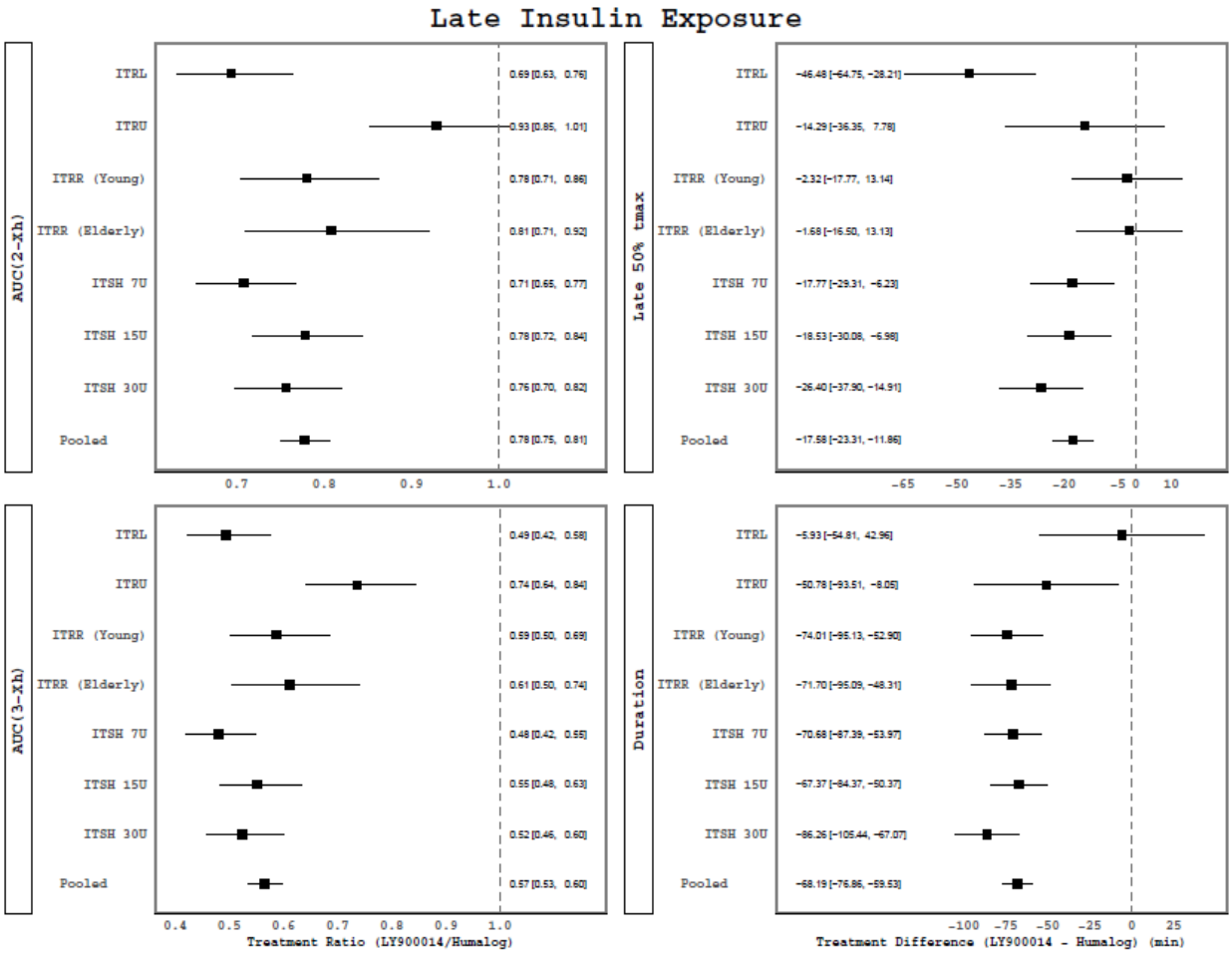
The accelerated absorption resulted in greater early insulin lispro exposure with LY900014 than with Humalog. The largest increase was observed in the first 15 minutes after injection. The treatment ratio between LY900014 and Humalog for AUC(0-15min) was 7.51 in the meta-analysis. Significant increases in exposure were also demonstrated at 30 minutes and 1 hour after injection. The treatment ratio between LY900014 and Humalog for the AUC(0-30min) and for the AUC(0-1h) were 2.97 and 1.52, respectively, in the meta-analysis (Figure 14). Overall, the results indicate that LY900014 provided approximately 8 times, 3 times, and 1.5 times more insulin lispro exposure after administration than Humalog for the first 15, 30 and 60 minutes, respectively.

Figure 14. Mean treatment difference or ratio and 95% CI for the early insulin lispro PK parameters in adults in individual studies and in the meta-analysis.



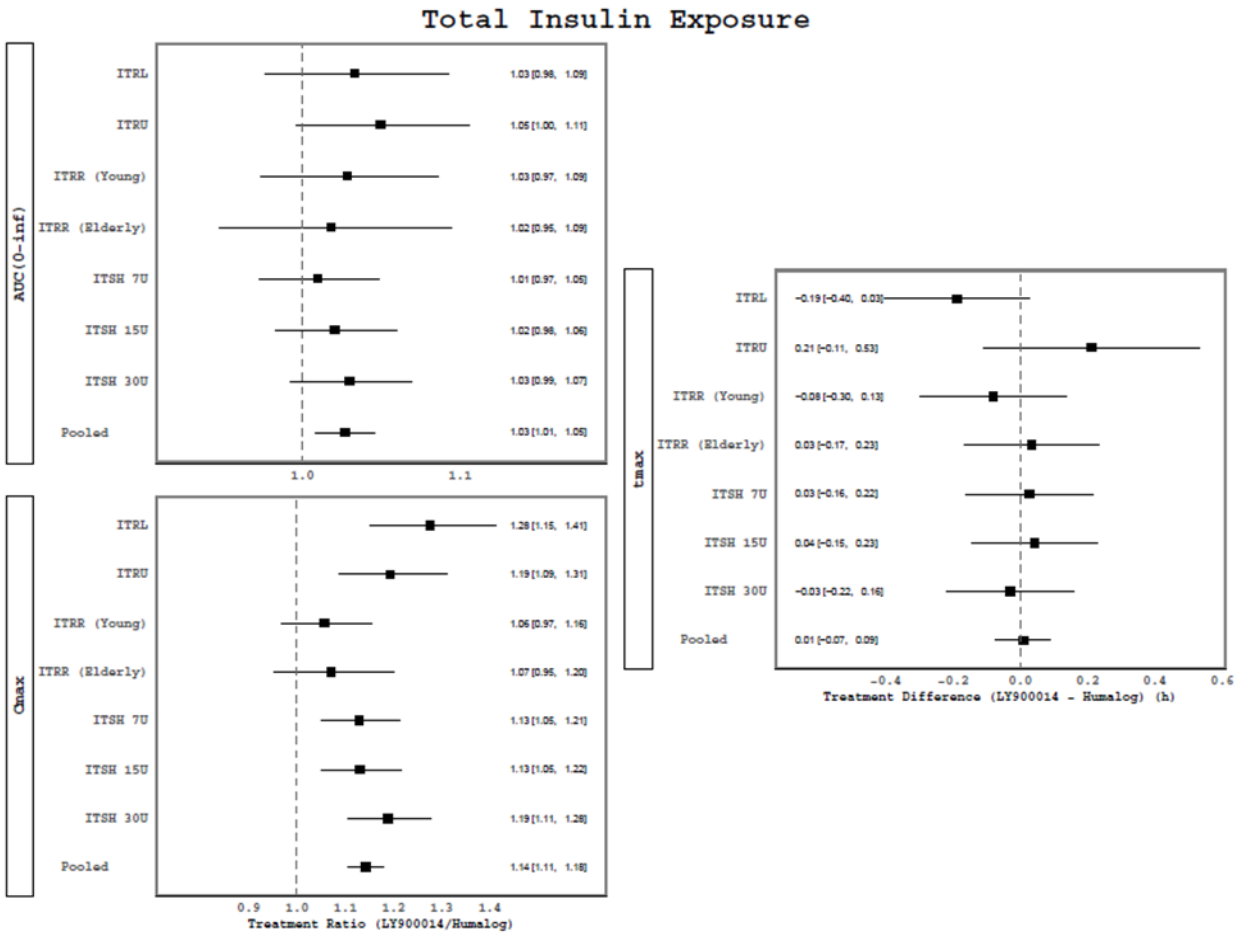
LY900014 reduced the late insulin lispro exposure characterised using the duration of insulin lispro exposure in the serum, the timing of the late 50% t_{max}, and the insulin lispro exposure from two hours to the end of PK sampling period (AUC[2h-Xh]), and three hours to the end of PK sampling period (AUC[3h-Xh]). A statistically significant reduction was consistently shown in the insulin lispro exposure after 3 hours where the treatment ratio between LY900014 and Humalog was 0.57 in the meta-analysis (Figure 15). This indicates that LY900014 had 43% less insulin lispro exposure after 3 hours than observed following Humalog administration.

Figure 15. Mean treatment difference or ratio and 95% CI for the late insulin lispro PK parameters in adults in individual studies and in the meta-analysis.



The total insulin lispro exposure (AUC[0-∞]) and the time to maximum concentration (t_{max}) were comparable between LY900014 and Humalog in the individual studies and in the meta-analysis. The accelerated insulin lispro absorption rate following LY900014 administration resulted in a slightly higher C_{max} compared to Humalog, which was a 14% increase from the meta-analysis (Figure 16).

Figure 16. Mean treatment difference or ratio and 95% CI for the overall insulin lispro PK parameters in adults in individual studies and in the meta-analysis.



Pharmacokinetics of LY900014 vs Humalog: Continuous SC insulin infusion

Study ITSC was a 4-period, patient- and investigator-blind, randomized, crossover study in patients with T1D to evaluate the insulin lispro PK and GD characteristics of LY900014 over 3 days with continuous subcutaneous insulin infusions (CSII) compared with that of Humalog using a Medtronic MiniMed 640G pump. The primary objective was to evaluate the difference in insulin lispro PK when LY900014 and Humalog are administered as different test bolus doses using an insulin pump to patients with T1DM during a breakfast mixed meal tolerance test (MMTT).

Each patient was randomized to 1 of 4 treatment sequences comprising CSII of LY900014 or Humalog, with different combinations of the modes of administration of the bolus doses relative to the breakfast, lunch, and dinner meals using an insulin pump. The bolus dose of insulin lispro (LY900014 or Humalog) was individualized per patient to cover the carbohydrate content of the meals and was maintained over the study periods for each treatment. The modes of administration were as follows:

- Mode 1: bolus dose was administered as a standard dual-wave (SD) bolus (50% immediate bolus delivery [speed = 1.5 U/minute] and 50% as a square wave over 3 hours)
- Mode 2: bolus dose was administered as a standard single-wave (SS) bolus (speed = 1.5 U/minute)
- Mode 3: bolus dose was administered as a rapid single-wave (RS) bolus (speed = 15 U/minute)

- Mode 4: bolus dose was administered as a rapid dual-wave (RD) bolus (50% immediate bolus delivery [speed = 15 U/minute] and 50% as a square wave over 3 hours)

The mean insulin lispro exposure over time on Days 1 and 3 after LY900014 and Humalog administration using a SS bolus or a SD bolus during the breakfast MMTT is presented in Figure 17 and Figure 18, respectively.

Following a SS bolus, LY900014 reduced the early 50% t_{max} by approximately 8.5 minutes (37%) on Day 1 (p <0.0001) and by approximately 5.3 minutes (32%) on Day 3 (p <0.0001) compared to Humalog, and statistically significantly (p<0.05) higher AUC(0-15min) and AUC(0-30min) values on Day 1 and Day 3 were observed following LY900014 administration compared to Humalog. There was no statistically significant difference in t_{max}, C_{max}, AUC(0-1h), AUC(0-5h), AUC(0-tlast], change from baseline (CFB) AUC(0-5h), and late 50% tmax between LY900014 and Humalog for either Day 1 or 3.

Following a SD bolus, LY900014 reduced the early 50% t_{max} by approximately 7.5 minutes (39%) on Day 1 (p=0.0011) and by approximately 3.2 minutes (26%) on Day 3 (p=0.0422) compared to Humalog, and statistically significantly (p<0.05) higher AUC(0-15min) and AUC(0-30min) values on Day 1 and Day 3 were observed following LY900014 administration compared to Humalog. There was no statistically significant difference in t_{max}, C_{max}, AUC(0-1h), AUC(0-5h), CFB AUC(0-5h), and late 50% t_{max} between LY900014 and Humalog for either Day 1 or 3.

Figure 17. Mean insulin lispro concentration (±SE) versus time (top) and the first hour postdose (bottom) following a standard single-wave (SS) bolus dose on Day 1 (left) and Day 3 (right) for Humalog and LY900014 (Study ITSC).

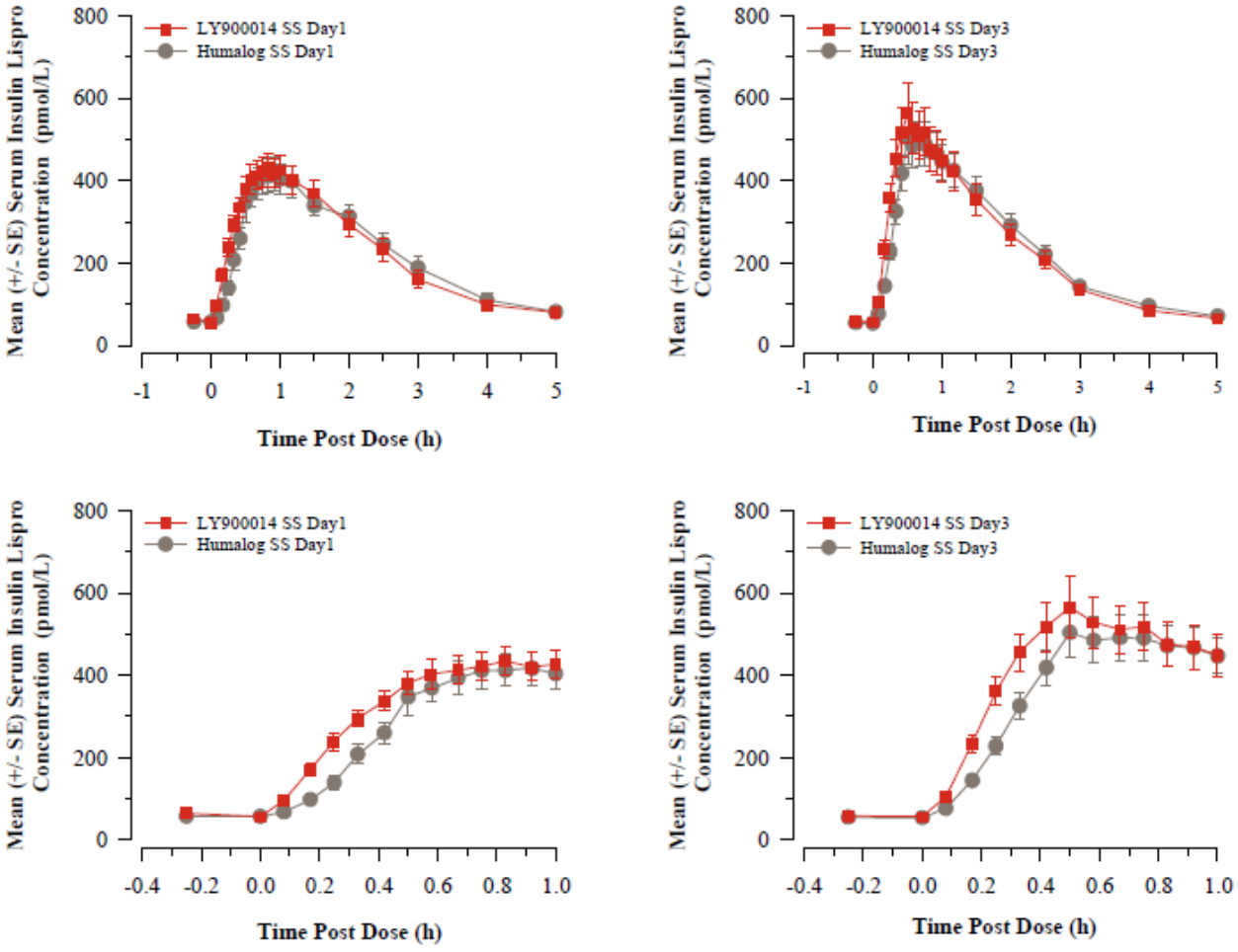
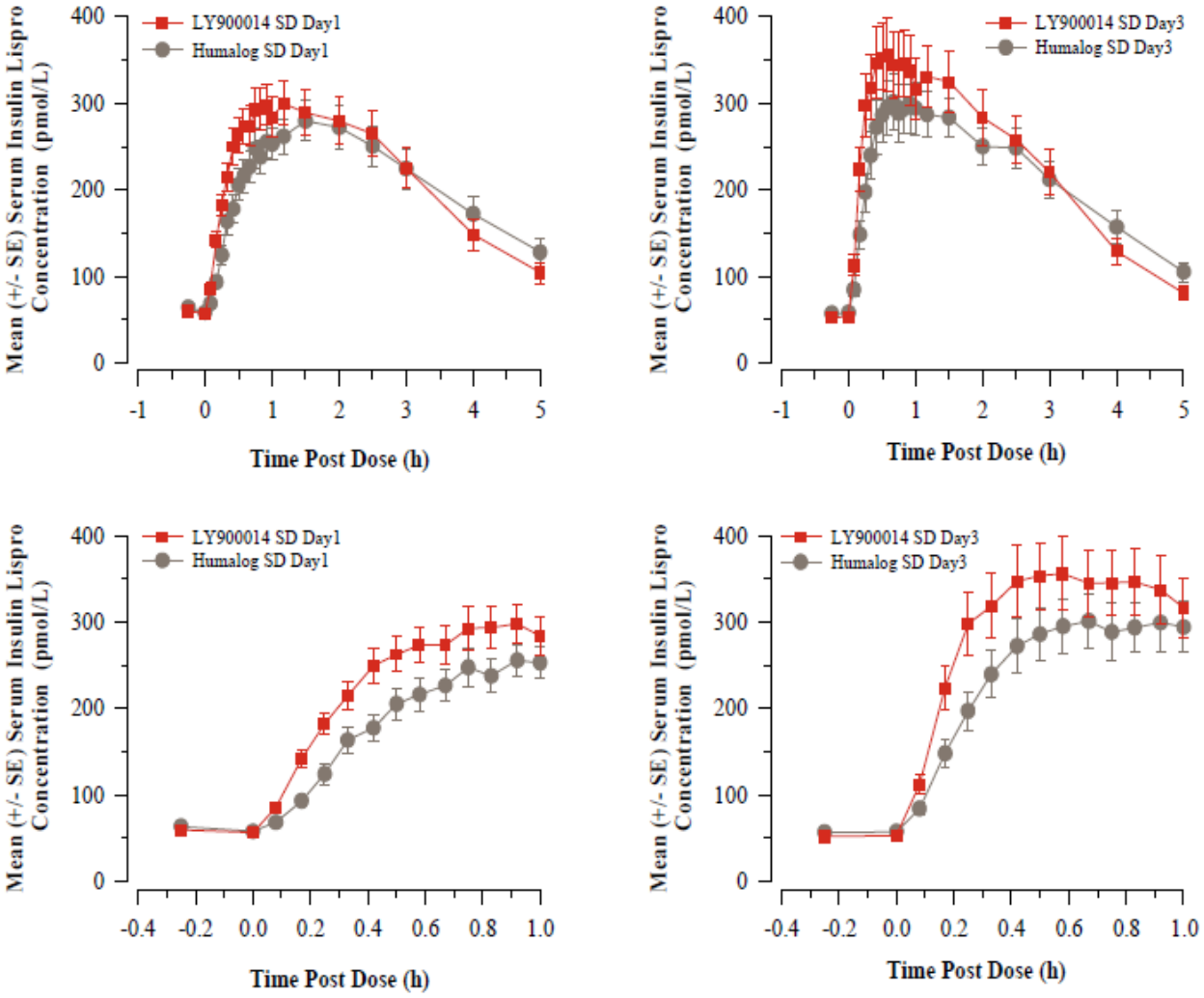


Figure 18. Mean insulin lispro concentration (±SE) versus time (top) and the first hour (bottom) following a standard dual-wave (SD) bolus dose on Day 1 (left) and on Day 3 (right) for Humalog and LY900014 (Study ITSC).



Special populations

The evaluation whether the difference between LY900014 and Humalog in PK and pharmacodynamic parameters is similar between elderly (≥65 years) and younger adults (18 to 45 years) with T1D was an exploratory objective of study ITRR (see above). There were no statistically significant age group-by-treatment interactions, indicating that the treatment effect between LY900014 and Humalog was similar for elderly and younger adults.

Overall 64 subjects aged 65 to 74 and one subject aged 75 to 84 years, none ≥85 years, were included in the clinical pharmacology studies.

The number of elderly persons included in the clinical pharmacology studies is summarised in the table below:

Study	Age 65-74 Number of elderly/total number of subjects	Age 75-84 Number of elderly/total number of subjects	Age 85+ Number of elderly/total number of subjects
I8B-MC-ITRF	0/30	0/30	0/30
I8B-MC-ITRL	0/32	0/32	0/32
I8B-MC-ITRQ	0/49	0/49	0/49
I8B-MC-ITRR[a]	37/79	1/79	0/79
I8B-MC-ITRT	0/28	0/28	0/28
I8B-MC-ITRU	13/38	0/38	0/38
I8B-MC-ITRV	2/36	0/36	0/36
I8B-MC-ITRW	10/36	0/36	0/36
I8B-MC-ITRZ	0/31	0/31	0/31
I8B-MC-ITSC	1/24	0/24	0/24
I8B-MC-ITSH	0/42	0/42	0/42
I8B-MC-ITSS	1/68	0/68	0/68
Total	**64/493**	**1/493**	**0/493**

Abbreviations: CSII = continuous subcutaneous insulin infusion; GD = glucodynamics; PK = pharmacokinetics; SC = subcutaneous; T1D = type 1 diabetes.

[a] ITRR was a crossover study that compared the PK and GD of insulin lispro from LY900014 and Humalog following administration of a single 15 U SC dose in elderly and younger adults with T1D who were either on multiple daily insulin injections or on CSII. The elderly group included patients with T1D who were aged at least 65 years.

Pharmacokinetic data for paediatric subjects is not yet available.

The effect of renal and hepatic impairment is expected to be similar to what has been observed for Humalog earlier. Pharmacokinetics of LY900014 was not investigated in these populations.

Dedicated studies investigating the effect of race and gender on pharmacokinetics were not conducted for LY900014. Covariate analysis using the population PK model, indicated that there was no impact of race and gender on the pharmacokinetics.

Covariate analysis using the population PK model estimated an increase of 16.5% in the insulin lispro clearance for subjects with anti-insulin antibodies detected at baseline.

Pharmacokinetic interaction studies

Drug interaction studies were not conducted for LY900014.

2.4.3. Pharmacodynamics

Mechanism of action

Insulin lispro is a well-known rapid-acting insulin analogue. LY900014 is a new formulation of insulin lispro for subcutaneous (SC) use and for intravenous (IV) use to improve glycaemic control in patients with type 1 diabetes mellitus (T1D) or type 2 diabetes mellitus (T2D).

The Applicant holds two duplicate licences for insulin lispro: Humalog (EU/1/96/007/) and Liprolog (EU/1/01/195/001) approved in 1996 and 2001 respectively. Lispro insulin used in LY900014 is the same active ingredient used in Humalog and Liprolog. Two excipients in LY900014 enable by independent mechanisms acceleration of the absorption of insulin lispro from the site of subcutaneous injection resulting in a faster insulin time-action profile:

- Enhanced absorption of insulin lispro through increased local vasodilation, due to the addition of a microdose of treprostinil as an excipient in the formulation.
- Speeding absorption of insulin through enhanced local vascular permeability, which is achieved by addition of the excipient sodium citrate in the formulation.

The primary activity of insulin and insulin analogues is the regulation of glucose metabolism. They exert their action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose (BG) level by stimulating peripheral glucose uptake by skeletal muscle cells and adipocytes, and by inhibiting hepatic glucose production. Other actions of insulin include inhibition of lipolysis and proteolysis, and regulation of gene expression.

Once insulin lispro in LY900014 is absorbed into the systemic circulation, it is assumed that the pharmacodynamic action is the same as of insulin lispro in Humalog and Liprolog.

Treprostinil is a prostacyclin analogue that has been separately approved in several EU countries as a drug for the treatment of pulmonary arterial hypertension. Systemic exposure to treprostinil in clinical pharmacology studies was negligible. Treprostinil concentrations slightly above the LLOQ (0.0100 ng/mL) were observed at 2.5 and 5 minutes following IV bolus injection of a 15U dose of LY900014, but not at 10 minutes and later. Treprostinil levels were below the LLOQ following SC administration.

Primary and Secondary pharmacology

The effect of LY900014 on blood glucose levels were investigated and compared to Humalog in healthy subjects and patients with T1D and T2D. The methods included the glucose clamp technique, which is the preferred method to assess the time-action profile of insulins, and a mixed meal tolerance test (MMTT), which enables to investigate the glucose-lowering properties of insulins in a clinically relevant but still standardised setting. Investigation of pharmacokinetics was the primary objective of the studies; investigation of glucodynamics (GD) was a secondary objective. All studies were conducted as cross-over studies; see Table 8 and section 3.3.1 Pharmacokinetics above. The key glucodynamic parameters for the clamp studies are summarised in Table 9.

Table 9. Key (Weight-Normalized) Glucodynamic Parameter Definitions of glucose clamp studies

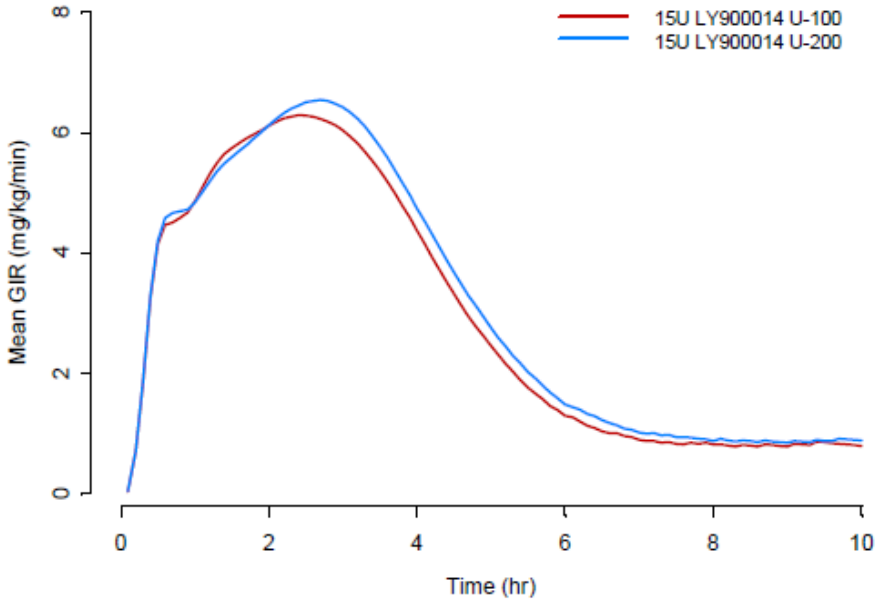
Parameter	Units	Definition
G_{tot}	mg/kg/min	total amount of glucose infused over the duration of the clamp
G_{tot}(0-30min)	mg/kg/min	total amount of glucose infused over first 30 minutes post injection
G_{tot}(0-1h)	mg/kg/min	total amount of glucose infused over first 1 hour post injection
G_{tot}(0-2h)	mg/kg/min	total amount of glucose infused over first 2 hours post injection
G_{tot}(2-End)	mg/kg/min	total amount of glucose infused from 2 hours postdose until the end of the clamp
G_{tot}(3-End)	mg/kg/min	total amount of glucose infused from 3 hours postdose until the end of the clamp
G_{tot}(4-End)	mg/kg/min	total amount of glucose infused from 4 hours postdose until the end of the clamp
tR_{max}	min	time to maximum glucose infusion rate
R_{max}	mg/kg/min	maximum glucose infusion rate
Early 50% tR_{max}	min	time to half-maximal glucose infusion rate before maximum glucose infusion rate
Late 50% tR_{max}	min	time to half-maximal glucose infusion rate after maximum glucose infusion rate
T_{onset}	min	time to onset of insulin action as defined as when blood glucose drops by 0.3 mmol/L (5 mg/dL) from baseline
Duration of Action	min	calculated by subtracting the T_{onset} from the end of the clamp ($tGIR_{last}$)

Effect of formulation strength on glucodynamics

Glucodynamic effects of LY900014 200 U/mL formulation and LY900014 100 U/mL formulation during euglycaemic clamp were investigated in healthy subjects in study ITSS.

SC injection of 15 U dose of LY900014 200 U/mL and LY900014 100 U/mL resulted in comparable glucose infusion rate (GIR) versus time profiles (Figure 19). The primary GD parameters Gtot and Rmax were comparable: the ratio of geometric LS means (90% CI) was 1.06 (1.01, 1.11) and 1.03 (1.00, 1.07) for Gtot and Rmax, respectively. Results for exploratory GD parameters also supported the conclusion that glucodynamic effect is similar following SC injection of LY900014 200 U/mL and LY900014 100 U/mL formulations.

Figure 19. Mean locally weighted scatterplot smoothing fits of weight-normalized glucose infusion rate versus time for a subcutaneous 15 U dose of 100 units/mL LY900014 compared to 200 units/mL LY900014 (Study ITSS).



Abbreviations: GIR = glucose infusion rate; hr = hour; U = unit.

Impact of injection site on glucodynamics

The effect of SC injection site (abdomen, deltoid, thigh) of LY900014 on glucodynamics during euglycaemic clamp was investigated in study ITRT. The primary GD parameters were Gtot and Rmax.

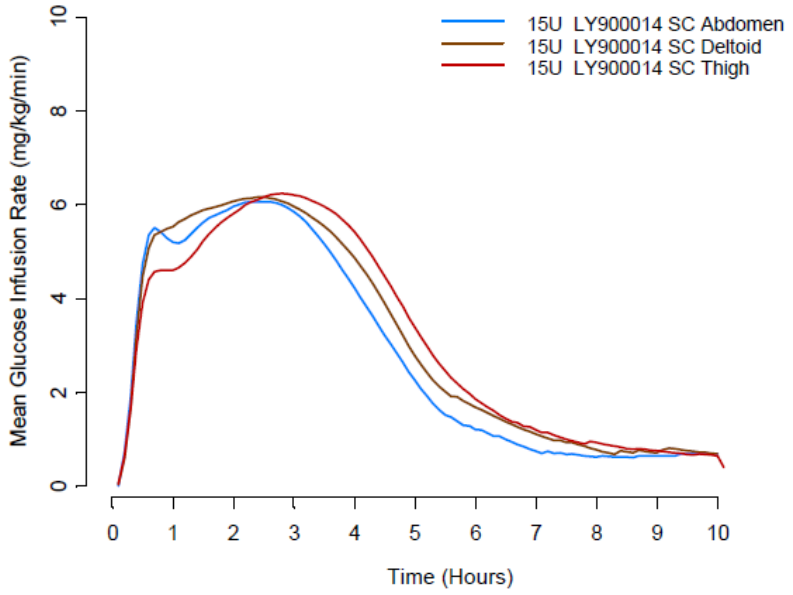
The mean LOESS-fitted GIR profiles following injection of 15 U of LY900014 into the abdomen (N=25), deltoid (N=26), and thigh (N=26) are shown in in Figure 20. Following SC injection into the thigh, the GIR curve was slightly shifted to the right, in line with the observed slightly slower absorption from the thigh.

Geometric means of Gtot (1630 vs 1490 mg/kg) and Rmax (6.71 vs 6.36 mg/kg/min) were comparable for injection into deltoid vs abdomen. The median time of Rmax was also comparable between deltoid and abdomen (median of differences of tRmax 6.0 min; p=0.23). This is in line with the comparable concentration-time curves following injection into deltoid and abdomen.

Geometric means of Rmax (6.71 vs 6.36 mg/kg/min) were comparable for injection into the thigh vs abdomen, but the median time of Rmax was later following injection into the thigh (median of differences of tRmax 54.0 min; p=0.0003). This is in line with the slower absorption following injection into the thigh. Geometric mean of Gtot was 16% higher following injection into the thigh compared to abdomen (1730 vs 1490 mg/kg).

In statistical analyses for subjects that completed the study (i.e. had data for all injection sites; N=25) the ratio (90% CI) of geometric LS means for comparisons between deltoid vs abdomen were 1.09 (0.99, 1.20) and 1.05 (0.96, 1.15) for Gtot and Rmax, respectively. For comparisons between the thigh vs abdomen the ratio (90% CI) of GLS means were 1.14 (1.04, 1.25) and 1.03 (0.94, 1.13) for Gtot and Rmax, respectively.

Figure 20. Arithmetic mean LOESS-fitted GIR profiles during euglycaemic clamps for single SC injections of 15 U LY900014 into the abdomen, deltoid, and thigh (Study ITRT).



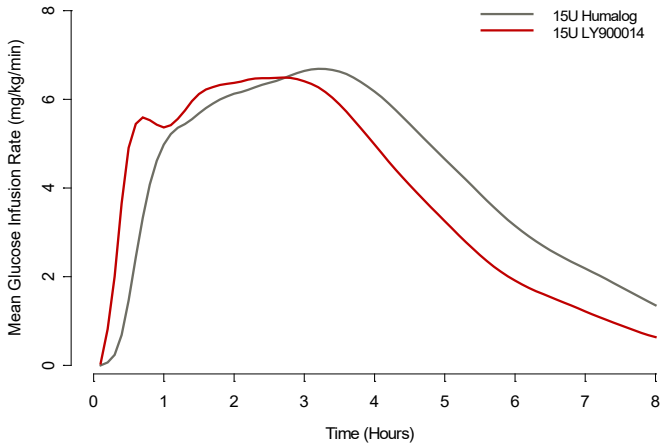
GIR = glucose infusion rate; **LOESS** = locally weighted scatterplot smoothing; **SC** = subcutaneous; **U** = units.

Glucodynamics of LY900014 vs Humalog: euglycaemic glucose clamp

Glucodynamics of LY900014 vs Humalog in healthy subjects were investigated in study ITRL. Mean locally weighted scatterplot smoothing (LOESS) fits of glucose infusion rate (GIR) versus time comparing a 15 U dose of LY900014 to 15 U Humalog are presented in Figure 21. Left shifting of the GIR curve can be seen, demonstrating earlier effect for LY900014 compared with Humalog.

The primary GD endpoints were early 50% tRmax, Gtot(0-30min), Gtot(0-1h), and Tonset, which describe early insulin action. LY900014 demonstrated an earlier glucose-lowering effect compared to Humalog these GD endpoints ($p<0.001$ for each). The geometric LS means of Gtot(0-30min) and Gtot(0-1h) for LY900014 vs Humalog were 53.63 vs 8.75 mg/kg and 85.39 vs 188.31 mg/kg, respectively. The medians of early 50% tRmax, and Tonset for LY900014 vs Humalog were 25.6 vs 49.4 min and 19.8 vs 34.8 min, respectively. The late 50% tRmax was reduced with LY90014 compared to Humalog. No difference between LY900014 and Humalog was observed for the Rmax. The total glucose infused over the clamp (Gtot) was slightly lower for LY900014 compared to Humalog (ratio of geometric LS means 0.92; 90% CI 0.85-0.99) but the 90% CI of the ratio was within the conventional equivalence range of 0.8 to 1.25.

Figure 21. Mean locally weighted scatterplot smoothing fits of weight-normalized glucose infusion rate vs time for a 15 U dose of LY900014 compared to a 15 U dose of Humalog (study ITRL).



Glucodynamics of LY900014 vs Humalog in elderly and young adult patients with T1D was investigated in study ITRR. The primary GD endpoints were early 50% tRmax, Gtot(0-30min), Gtot(0-1h), and Tonset, which describe early insulin action.

Mean LOESS fits of GIR vs time comparing a 15 U dose of LY900014 to 15 U Humalog are presented in Figure 22. Left shifting of the GIR curve of LY900014 compared with Humalog was observed in younger adults and in the elderly.

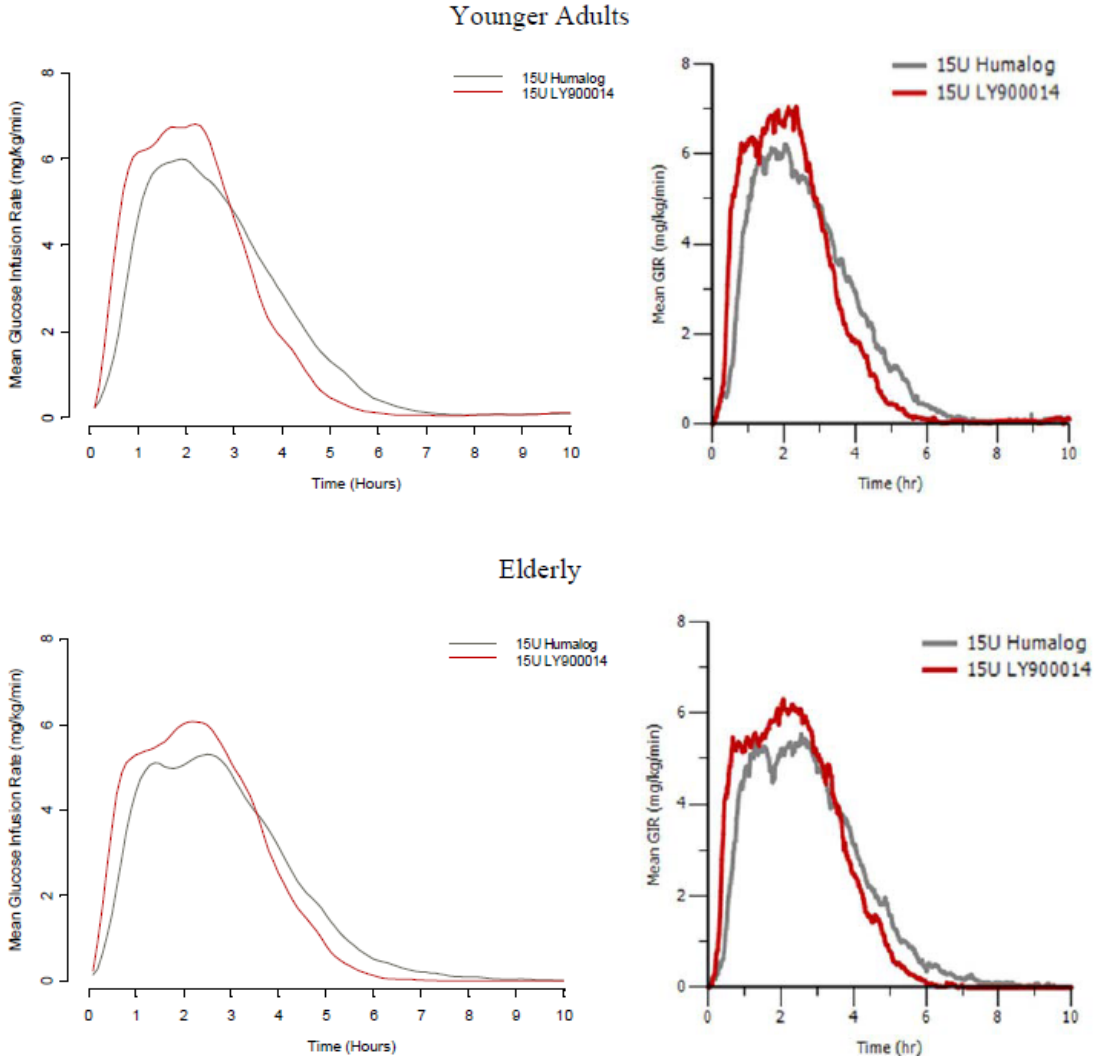
In younger adults, LY900014 demonstrated an earlier glucose-lowering effect compared to Humalog for each primary GD endpoint ($p<0.001$ for each; completers analysis, N=38). The least squares means of Gtot(0-30min), Gtot(0-1h), early 50% tRmax and Tonset for LY900014 vs Humalog were 40.78 vs 14.01 mg/kg, 198.75 vs 106.38 mg/kg, 33.35 vs 47.49 min, and 20.16 vs 31.38 min, respectively.

In the elderly, LY900014 demonstrated an earlier glucose-lowering effect compared to Humalog for each primary GD endpoint ($p<0.0156$ for each; completers analysis, N=35). The least squares means of Gtot(0-30min), Gtot(0-1h), early 50% tRmax and Tonset for LY900014 vs Humalog were 43.28 vs 13.64 mg/kg, 186.31 vs 110.23 mg/kg, 37.12 vs 46.84 min, and 18.56 vs 30.78 min, respectively.

LY900014 significantly reduced the late insulin action and shortened the duration of action compared to Humalog in younger adult and elderly patients with T1D.

In addition, the Rmax was slightly, but statistically significantly, higher following LY900014 compared to Humalog administration in both populations. The ratio (95% CI) of geometric LS means was 1.14 (1.04, 1.25) and 1.14 (1.03, 1.26) in younger adults and the elderly, respectively. The total amount of glucose infused during the clamp was comparable between Humalog and LY900014, however.

Figure 22. Mean locally weighted scatterplot smoothing fits of weight-normalized glucose infusion rate (left) and mean raw weight-normalized glucose infusion rate (right) vs time for a 15-U dose of LY900014 compared to a 15-U dose of Humalog in T1D patients; younger adults (top panels); elderly (bottom panels) [Study ITRR].



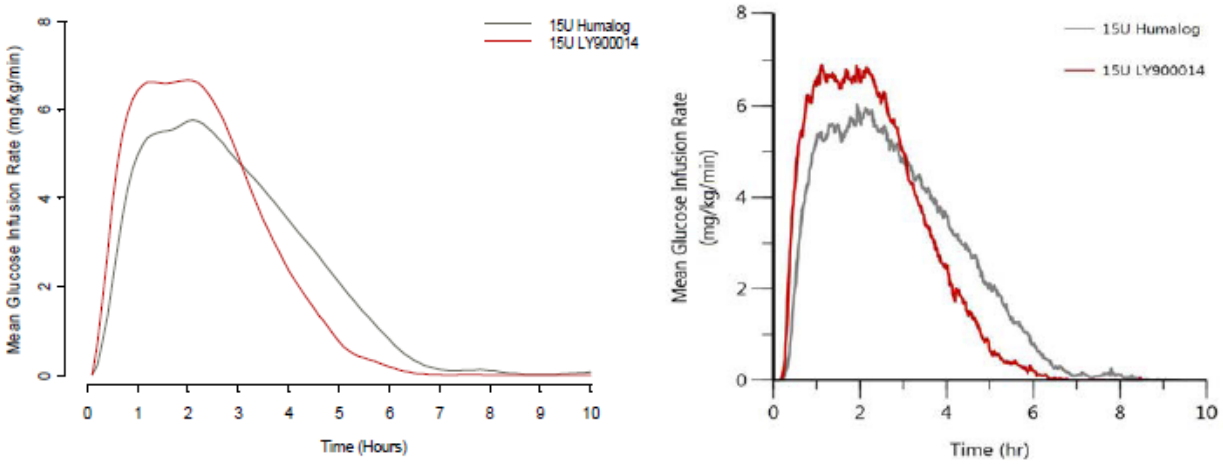
Glucodynamics of LY900014 vs Humalog in Japanese adult patients with T1D were investigated in study ITRZ. The primary GD endpoints were early 50% tRmax, Gtot(0-30min), Gtot(0-1h), and Tonset, which describe early insulin action.

Mean LOESS fits of GIR vs time comparing a 15 U dose of LY900014 to 15 U Humalog are presented in Figure 23. Left shifting of the GIR curve can be seen, demonstrating earlier effect for LY900014 compared with Humalog.

LY900014 demonstrated an earlier glucose-lowering effect compared to Humalog for each primary GD endpoint ($p<0.0006$ for each; completers analysis, N=30). The least squares means of Gtot(0-30min), early 50% tRmax and Tonset and geometric least squares mean Gtot(0-1h), for LY900014 vs Humalog were 41.24 vs 19.25 mg/kg, 30.05 vs 40.57 min, 17.04 vs 23.20 min and 187.46 vs 120.72 mg/kg, respectively. LY900014 significantly reduced the late insulin action, and shortened the duration of action compared to Humalog. In addition, the Rmax was slightly, but statistically significantly, higher following injection of LY900014 compared to Humalog. The ratio (95% CI) of geometric LS means for Rmax was

1.14 (1.01, 1.28). The total amount of glucose infused during the clamp was comparable between Humalog and LY900014, however.

Figure 23. Mean locally weighted scatterplot smoothing fits of weight-normalized glucose infusion rate (left) and mean raw weight-normalized glucose infusion rate (right) versus time for a 15-U dose of LY900014 compared to a 15-U dose of Humalog in Japanese patients with T1D (Study ITRZ).



Glucodynamics of LY900014 vs Humalog in patients with T2D were investigated in study ITRU. The primary GD endpoints were early 50% tRmax, Gtot(0-30min) and tonset, which describe early insulin action.

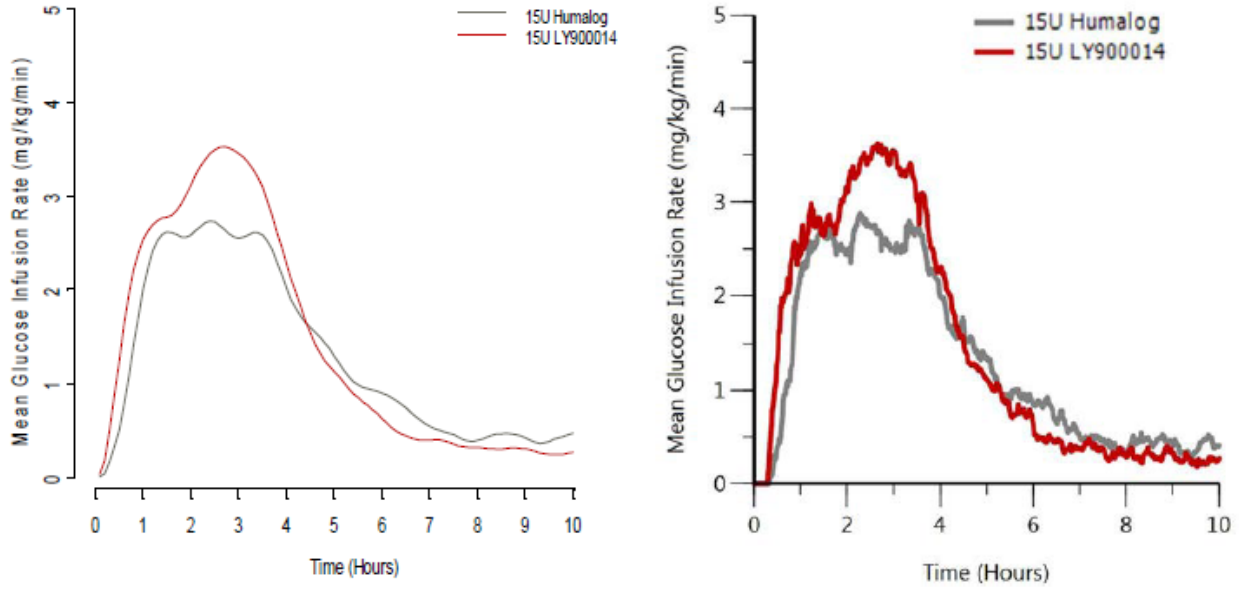
Mean LOESS fits of GIR vs time comparing a 15 U dose of LY900014 to 15 U Humalog are presented in Figure 24. A slight left shifting of the GIR curve can be seen, demonstrating earlier effect for LY900014 compared with Humalog.

LY900014 demonstrated an earlier glucose-lowering effect compared to Humalog for Gtot(0-30min) and tonset ($p<0.0001$ for each; completers analysis, N=37). The geometric LS means of Gtot(0-30min) and Tonset for LY900014 vs Humalog were 11.96 vs 2.82 mg/kg and 32.10 vs 44.99 min, respectively. However, the early 50% tRmax was comparable for LY900014 and Humalog: 53.78 min and 55.94 min, respectively.

Gtot(0-1h), which was a secondary GD parameter in study ITRU, supported the conclusion of increased early insulin action of LY900014: the geometric LS mean of Gtot(0-1h) was 73.35 and 41.95 mg/kg for LY900014 and Humalog, respectively. In addition, the late insulin action as measured as the amount of glucose infused from 4 hours to the end of the clamp was reduced by 19% with LY900014 compared to Humalog.

The ratio (95% CI) of GLS means of LY900014 and Humalog for Rmax and Gtot was 1.27 (1.11, 1.44) and 1.12 (1.00, 1.26), respectively.

Figure 24. Mean locally weighted scatterplot smoothing fits of weight-normalized glucose infusion rate (left) and mean raw weight-normalized glucose infusion rate (right) versus time for a 15 U dose of LY900014 compared to a 15 U dose of Humalog (Study ITRU).



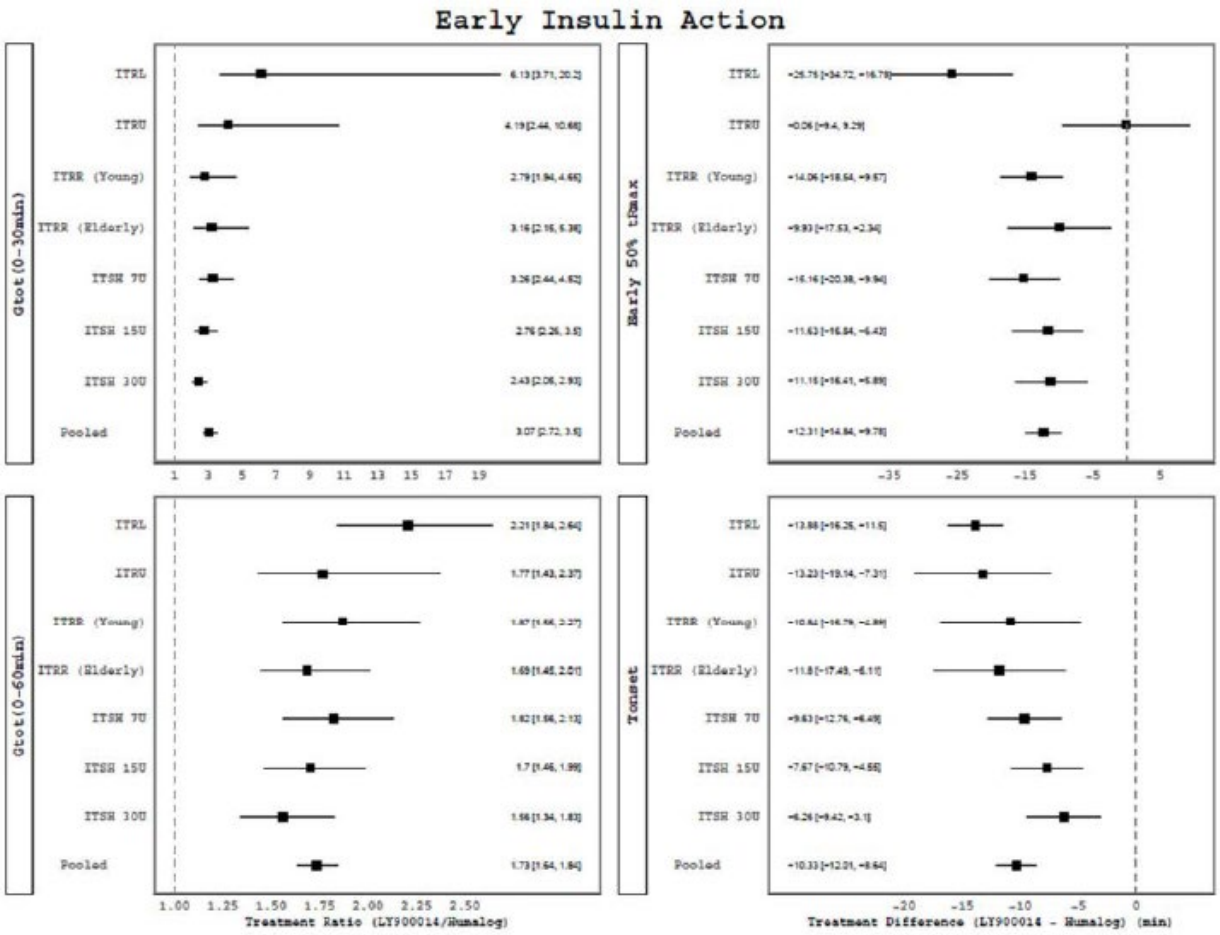
Meta-analysis of glucodynamics in glucose clamp studies: LY900014 vs Humalog

A meta-analysis was conducted by the Applicant to summarize the glucodynamics during an euglycaemic clamp after SC administration of a single dose of either a 7, 15 or 30 U LY900014 compared to Humalog. The meta-analysis included clinical pharmacology studies conducted in healthy subjects, patients with T1D and T2D. Studies included in the GD meta-analysis (ITRL, ITRU, ITRR, ITSH) used the final commercial formulation of LY900014, included Humalog as the comparator, collected GD data in a cross over study design, used similar timing for GD collection, and conducted comparisons between LY900014 and Humalog using the same dose level.

Forest plots were created that include the individual study 95% CIs using the analysis models presented in the clinical study reports. For the meta-analysis, GD parameters were compared between LY900014 and Humalog using a mixed effects model with treatment and study as fixed effects and subject as a random effect.

The early insulin action after LY900014 compared to Humalog was characterized using: the onset of insulin action, the early 50% tRmax, and the amount of glucose infused during the first 30 minutes [Gtot(0-30min)] and the first hour [Gtot(0-1h)] after injection. A consistent faster insulin action with LY900014 compared to Humalog was observed across these parameters for all study populations in the clinical pharmacology studies (Figure 25). The onset of action (Tonset) was 10.33 minutes earlier and the early 50% tRmax was reduced by 12.31 minutes with LY900014 compared to Humalog in the meta-analysis. This faster onset of insulin action resulted in greater amount of glucose infused during the early part of the clamp with LY900014 than with Humalog. The largest increase was observed in the first 30 minutes after injection. The treatment ratio between LY900014 and Humalog for Gtot(0-30min) was between 2.43 and 6.13 in the individual studies and 3.07 in the meta-analysis. This indicates that LY900014 provided approximately 3 times more insulin action in the first 30 minutes after administration than Humalog. Significant increases in early insulin action was also demonstrated at 1 hour after injection. The treatment ratio between LY900014 and Humalog for the Gtot(0-1h) was between 1.56 and 2.21 in the individual studies and 1.73 in the meta-analysis.

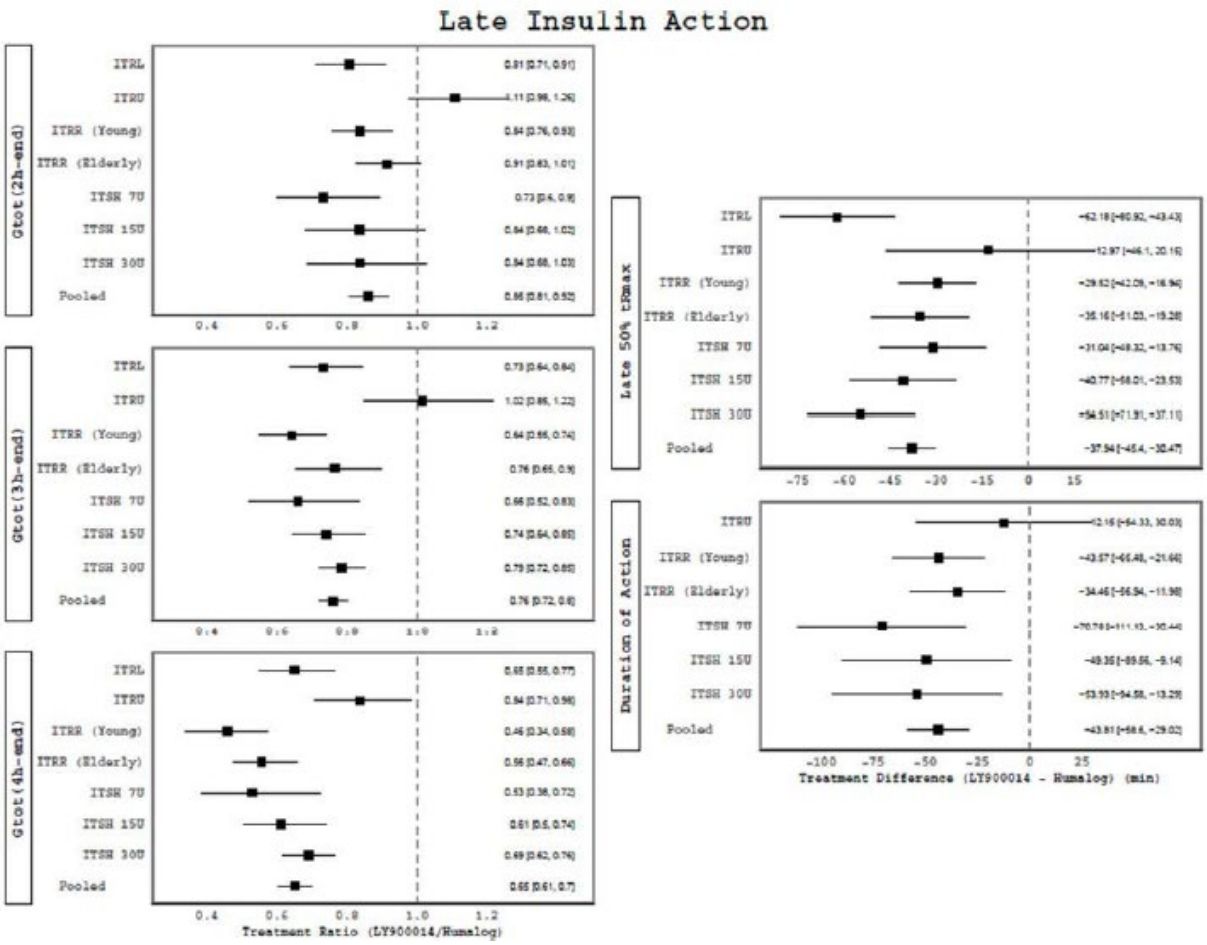
Figure 25. Mean treatment difference or ratio and 95% CI for the early insulin action glucodynamic parameters in adults in individual studies and in the meta-analysis.



The late insulin action after LY900014 compared to Humalog was characterized using: the duration of insulin action, the timing of the late 50% tRmax, and the amount of glucose infused after two hours [Gtot(2h-End)], three hours to the end of clamp [Gtot(3h-End)], and 4 hours to the end of clamp [Gtot(4h-End)]. The euglycaemic clamp was conducted over an 8-hour duration in Study ITRL, and over a 10-hour duration for all other studies in the meta-analysis.

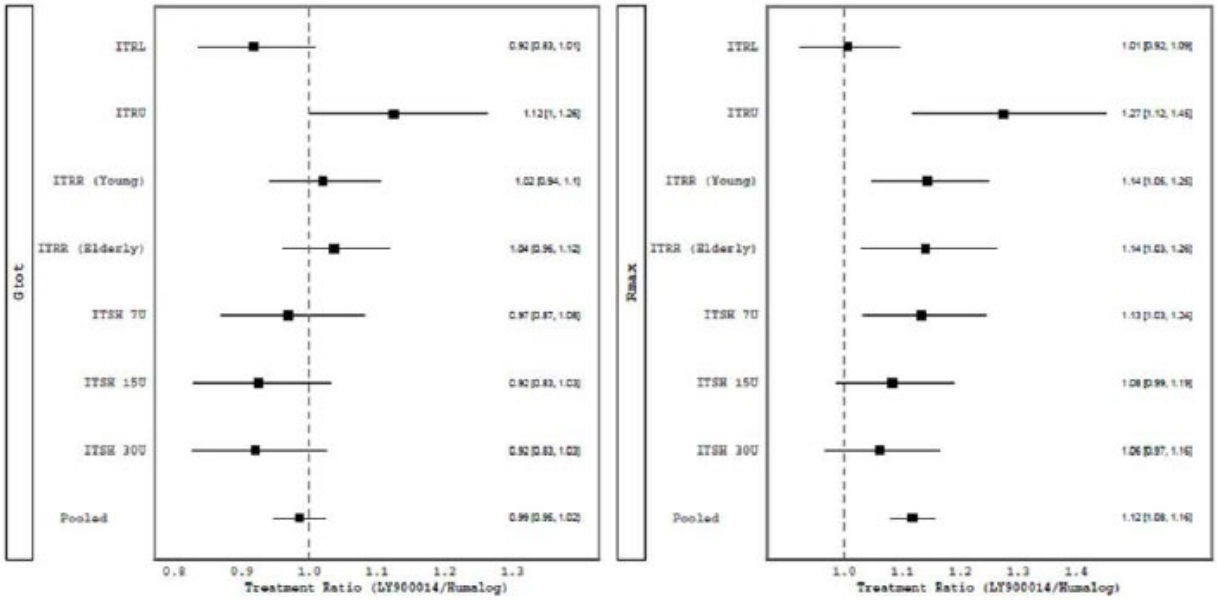
LY900014 reduced the late insulin action compared to Humalog across these parameters for all study populations (Figure 26). The most consistent reduction was shown in the Gtot(4h- End), which had a significant reduction in all of the individual studies. The treatment ratio between LY900014 and Humalog was between 0.46 and 0.84 in the individual studies and 0.65 in the meta-analysis. This indicates that LY900014 had 35% less insulin action after 4 hours than observed following Humalog administration.

Figure 26. Mean treatment difference or ratio and 95% CI for the late insulin action glucodynamic parameters in adults in individual studies and in the meta-analysis.



The overall insulin action (Gtot) was similar between LY900014 and Humalog, both in the individual studies and in the meta-analysis (Figure 27). The faster insulin action and shorter duration of insulin action following LY900014 administration resulted in a slightly higher Rmax compared to Humalog, which was a 12% increase from the meta-analysis.

Figure 27. Mean treatment ratio and 95% CI for the overall insulin action glucodynamic parameters in adults in individual studies and in the meta-analysis.



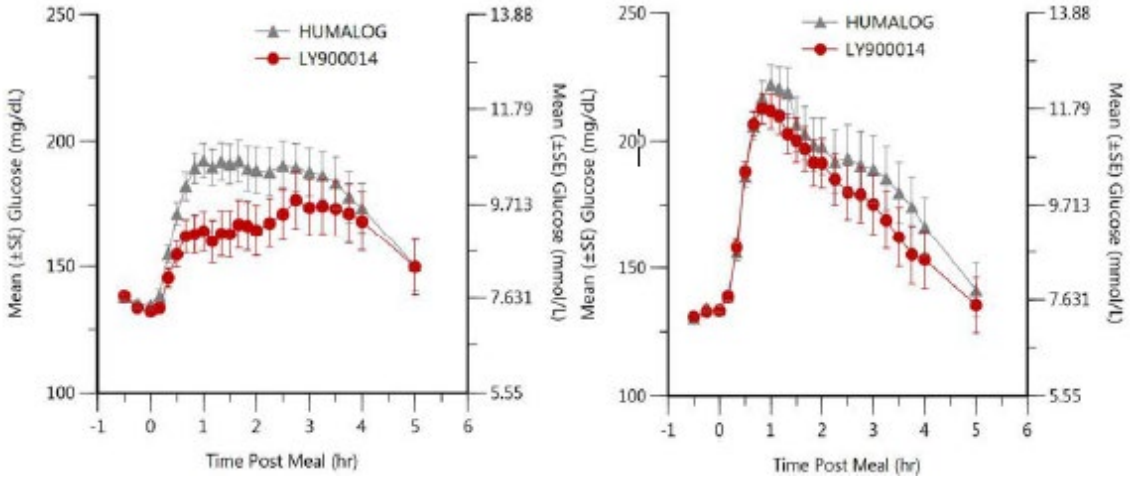
Glucodynamics of LY900014 vs Humalog: mixed meal tolerance test

A secondary objective of study ITRV was to evaluate the effect of injection-to-meal timings (SC injection immediately before the start of meal, and 20 minutes following the start of the meal) on the GD response to LY900014 compared to Humalog in patients with T1D.

The primary GD endpoints were the area under the baseline subtracted glucose concentration vs time curve from time 0 to 2hr [ΔAUC(0-2h)] and area under the baseline subtracted glucose concentration vs time curve from time 0 to 5hr post meal [ΔAUC(0-5h)]. Baseline was defined as the average of glucose concentration at 30, 15, and 0 minutes prior to the start of the meal. A liquid mixed meal with 100 g carbohydrates was used in the study. The dose of insulin lispro (LY900014 or Humalog) was individualized per patient to cover the carbohydrate content of the test meal and was maintained over the study periods for each treatment.

When the insulins were administered immediately before the start of the meal, LY900014 significantly reduced the early postprandial glucose excursions compared with Humalog, and a trend for reduced overall glucose excursion over 5-hour postprandial period was observed (Figure 28). The LSM of ΔAUC(0-2h) and ΔAUC(0-5h) for LY900014 vs Humalog were 2.55 vs 4.77 mmol·h·L^{-1} and 7.99 vs 11.74 mmol·h·L^{-1}, respectively. The change from baseline in blood glucose at 1h and 2h post-meal (LY900014 vs Humalog) was 1.63 mmol/L vs 3.15 mmol/L and 1.81 vs 3.07 mmol/L, respectively. When the insulins were administered at 20 minutes following the start of the meal, LY900014 showed a trend towards a lower postprandial glucose excursion compared to Humalog (not clinically meaningful).

Figure 28. Mean glucose concentration (±SE) versus time when dosed immediately before (left), and 20 minutes following the start of the meal (right) by treatment following a single SC dose of LY900014 or Humalog (Study ITRV).

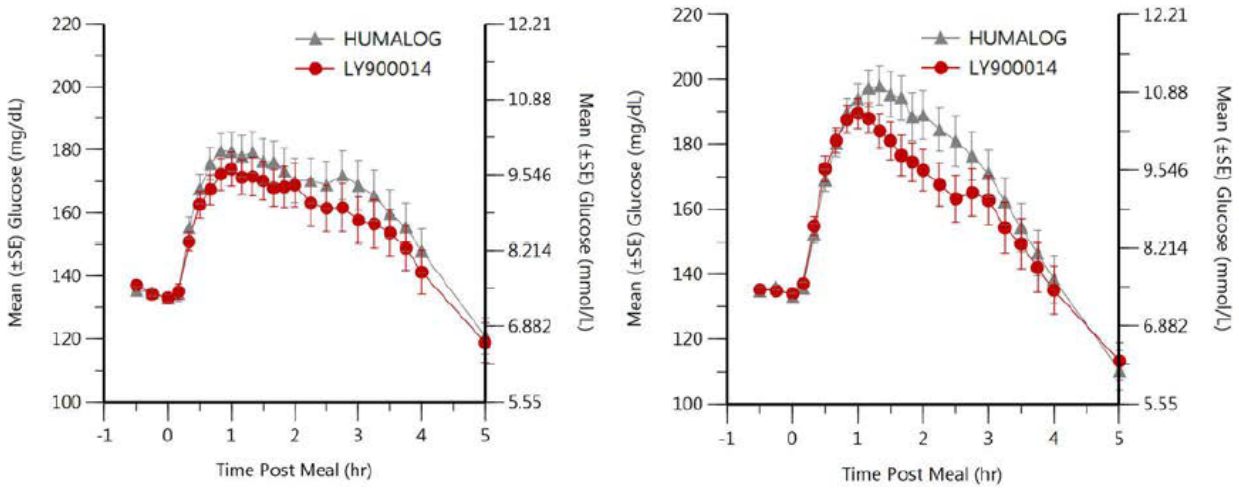


A secondary objective of study ITRW was to evaluate the effect of injection-to-meal timings (SC injection immediately before the start of meal, and 20 minutes following the start of the meal) on the GD response to LY900014 compared to Humalog in patients with T2D.

The primary GD endpoints were the area under the baseline subtracted glucose concentration vs time curve from time 0 to 2hr [ΔAUC(0-2h)] and area under the baseline subtracted glucose concentration vs time curve from time 0 to 5hr post meal [ΔAUC(0-5h)]. Baseline was defined as the average of glucose concentration at 30, 15, and 0 minutes prior to the start of the meal. A liquid mixed meal with 100 g carbohydrates was used in the study. The dose of insulin lispro (LY900014 or Humalog) was individualized per patient to cover the carbohydrate content of the test meal and was maintained over the study periods for each treatment.

LY900014 showed a trend towards a lower postprandial glucose excursion compared to Humalog at both of the meal-to-dose timing intervals (immediately before the start of the test meal and 20 minutes following the start of the test meal) (Figure 29). However, this did not reach statistical significance for the primary GD endpoints ΔAUC(0-2h) and ΔAUC(0-5h).

Figure 29. Mean glucose concentration (±SE) versus time post meal when dosed immediately before (left) and 20 minutes after the start of the test meal (right) by treatment following a single subcutaneous dose of LY900014 or Humalog (Study ITRW).

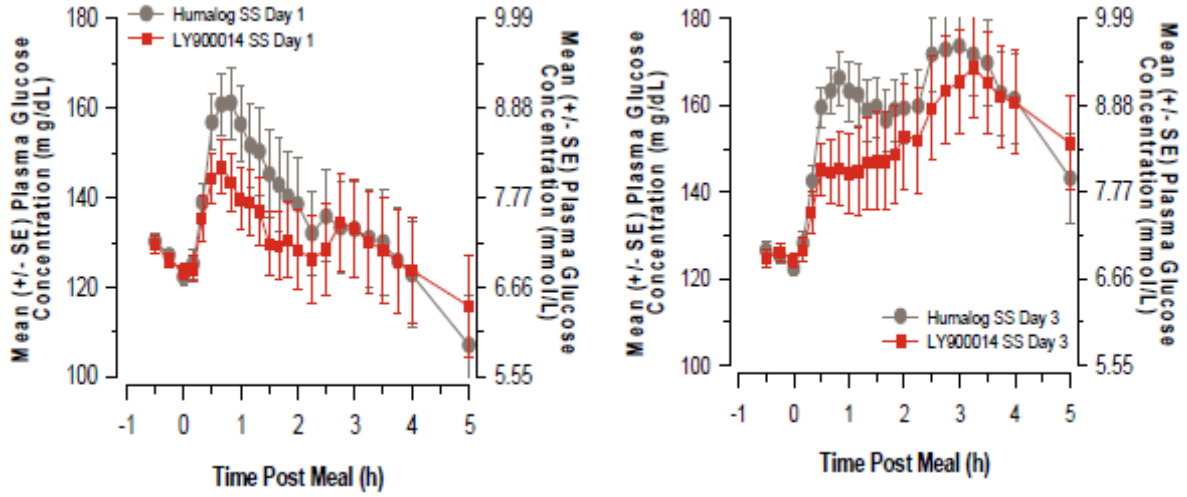


A secondary objective of study ITSC was to evaluate the difference in GD response when LY900014 and Humalog were administered as different test bolus doses with an insulin pump to patients with T1D during a breakfast meal test, and to compare the durability of GD response over 3 days when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1D during a breakfast meal test. LY900014 and Humalog bolus doses were given immediately before the breakfast test meal; see section 3.3.1 of this assessment report for further information on the bolus doses used in study ITSC.

The primary GD endpoints were the area under the baseline subtracted glucose concentration vs time curve from time 0 to 1h, 0 to 2h and 0 to 5h post breakfast [ΔAUC(0-1h), ΔAUC(0-2h) and ΔAUC(0-5h), respectively]. Baseline was defined as the average of glucose concentration at 30, 15, and 0 minutes prior to the start of the breakfast.

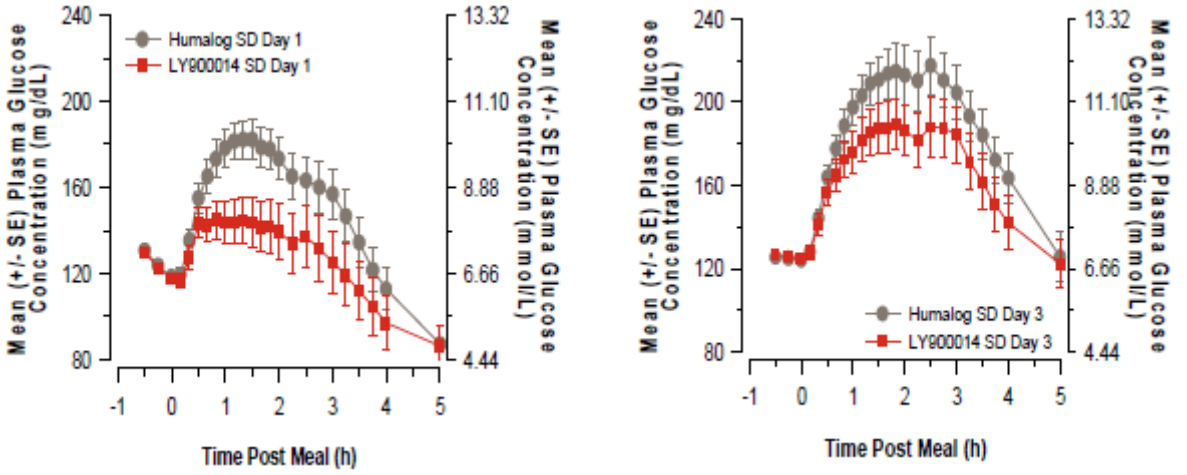
Mean postprandial glucose concentrations after LY900014 and Humalog with a standard single-wave (SS) bolus dose on Day 1 and Day 3 are presented in Figure 30. On Day 1, the ratio (90% CI) of LS means (LY900014:Humalog) was 0.55 (0.27, 0.83), 0.38 (0.03, 0.70) and 0.72 (0.30, 1.34) for ΔAUC(0-1h), ΔAUC(0-2h) and ΔAUC(0-5h), respectively, and on Day 3, the ratio (90% CI) of LS means was 0.60 (0.32, 0.82), 0.67 (0.31, 0.94), and 1.11 (0.82, 1.47). Data post intervention for hypo- or hyperglycaemia is excluded from these analyses.

Figure 30. Mean glucose concentration (±SE) versus time between Humalog and LY900014 following a standard single-wave bolus dose on Day 1 (left) and Day 3 (right) (Study ITSC).



Mean postprandial glucose concentrations after LY900014 and Humalog with a standard dual-wave (SD) bolus dose on Day 1 and Day 3 are presented in Figure 31. On Day 1, the ratio (90% CI) of LS means (LY900014:Humalog) was 0.45 (0.21, 0.65), 0.39 (0.15, 0.58) and 0.80 (0.52, 1.16) for ΔAUC(0-1h), ΔAUC(0-2h) and ΔAUC(0-5h), respectively, and on Day 3, the ratio (90% CI) of LS means was 0.74 (0.54, 0.95), 0.72 (0.55, 0.90), and 0.89 (0.68, 1.16). Data post intervention for hypo- or hyperglycaemia is excluded from these analyses.

Figure 31. Mean glucose concentration (±SE) versus time between Humalog and LY900014 following a standard dual-wave (SD) bolus dose on Day 1 (left) and Day 3 (right) (Study ITSC).



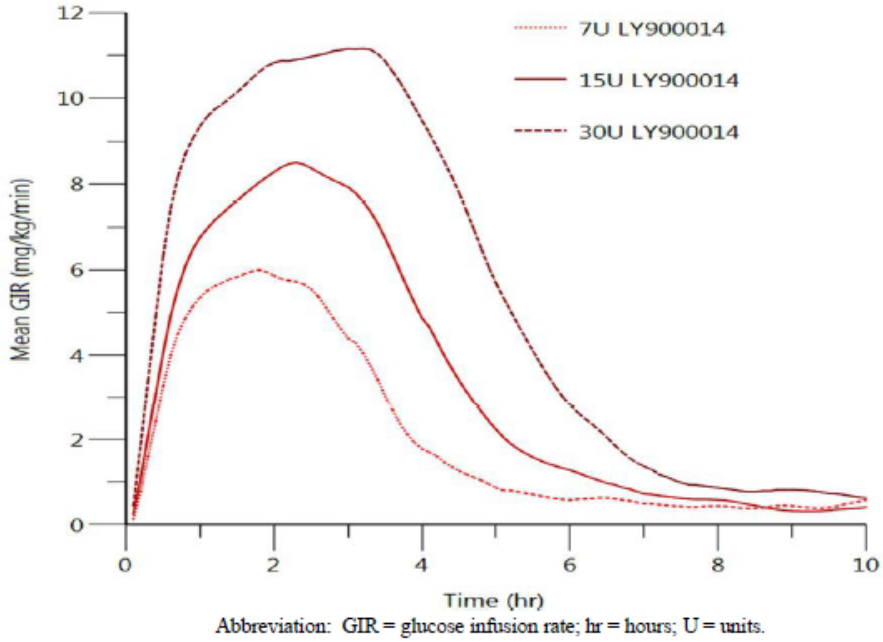
Dose-response relationship

Glucodynamics following 7 U, 15 U and 30 U SC injection of LY900014 was investigated in healthy subjects and compared to GD of Humalog in a randomised, subject- and investigator-blind, 6-period complete crossover euglycaemic clamp study ITSH.

Figure 32 presents the mean LOESS fits of glucose infusion rate versus time for LY900014 for each dose level. The mean LOESS GIR profile increased per dose level following administration of LY900014, indicating greater insulin action with increasing dose. The increase in Rmax and Gtot was less than dose proportional (Figure 33), however, indicating that the higher doses approached the top of the dose-response curve in the study population of healthy, presumably insulin-sensitive subjects. Notably,

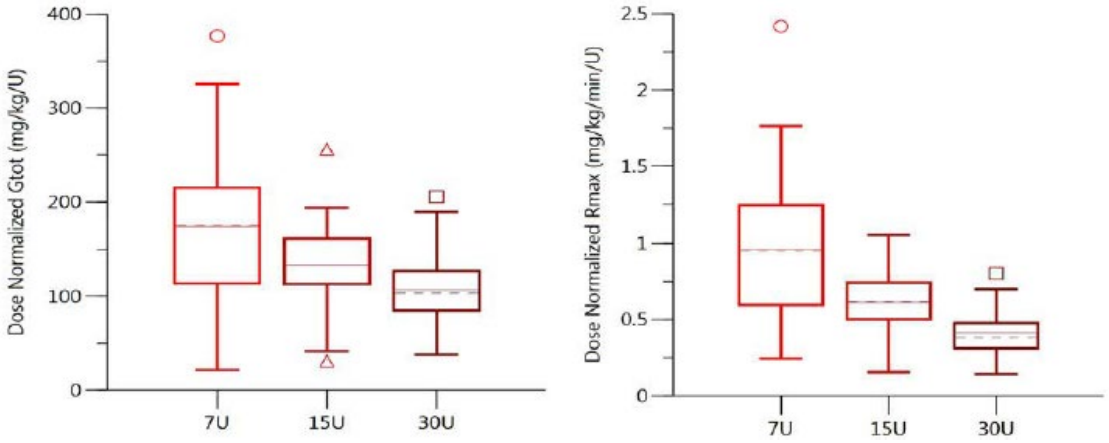
at each dose level, the total amount of glucose infused over the duration of the clamp was similar for LY900014 and Humalog, and left shifting of the GIR curve was observed (Figure 34).

Figure 32. Mean locally weighted scatterplot smoothing fits of weight-normalized glucose infusion rate versus time for a 7-, 15-, and 30-U dose of LY900014 (Study ITSH).



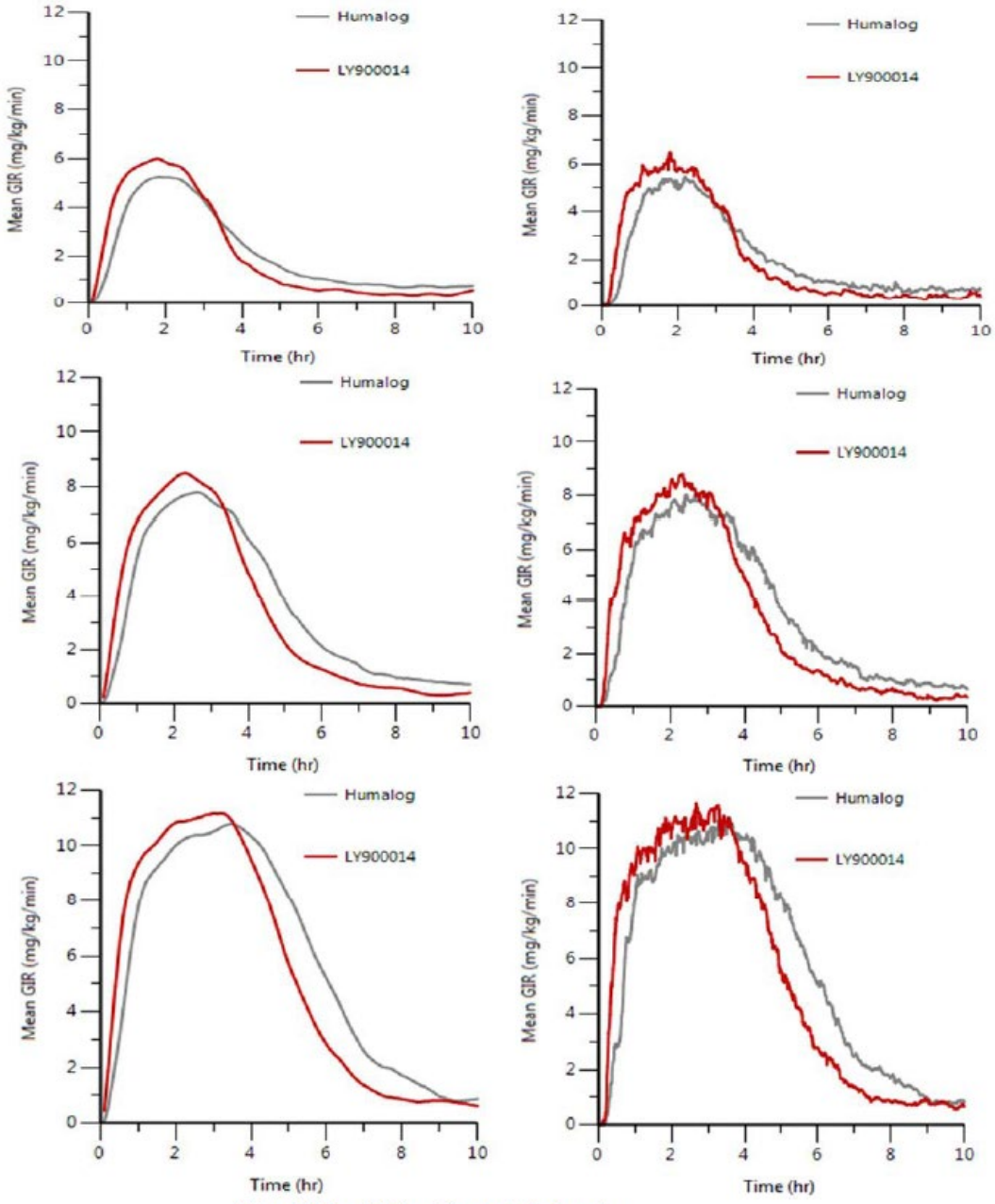
Abbreviation: GIR = glucose infusion rate; hr = hours; U = units.

Figure 33. Boxplots for dose-normalised LY900014 glucodynamic parameters for single SC injections of 7, 15, and 30 U LY900014 in healthy subjects (left: Gtot; right: Rmax).



Gtot = total amount of glucose infused; **Rmax** = maximum glucose infusion rate.
Boxplot dashed lines represent the medians; solid lines represent the means. The bottom and top of the boxes represent the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 of the interquartile range of the lower quartile and the highest value still within 1.5 of the interquartile range of the upper quartile.

Figure 34. Mean locally weighted scatterplot smoothing fits of weight-normalised glucose infusion rate (left panels) and mean weight-normalised raw glucose infusion rate (right panels) vs time for a 7 (top), 15 (middle), and 30 U (bottom) dose of LY900014 and Humalog (Study ITSH).



Abbreviation: GIR = glucose infusion rate.

Clinical studies investigating secondary pharmacology and pharmacodynamic drug interactions of insulin lispro were not conducted for LY900014.

2.4.4. Discussion on clinical pharmacology

Bioanalytical methods used in the clinical studies were, overall, appropriate.

Overall, the design of clinical pharmacology studies was adequate. Clinical study reports do not indicate any misconduct. Pharmacokinetics and pharmacodynamics of the commercial LY900014 100 U/mL

formulation were thoroughly investigated in healthy subjects and in the target population (patients with T1D and T2D). Study reports of several clinical pharmacology trials conducted with developmental formulations were provided by the Applicant, which is acknowledged. Results of these studies are not essential for the benefit/risk assessment of the final formulation, however, and they are not described in this assessment report.

Comparable pharmacokinetics and pharmacodynamics between LY900014 200 U/mL and LY900014 100 U/mL formulations was demonstrated in a euglycaemic glucose clamp study in healthy subjects. Benefit/risk conclusions on the LY900014 100 U/mL formulation used in the pivotal phase 3 studies can be extrapolated to the LY900014 200 U/mL formulation. Of note, according to the proposed SmPC, the 200 U/mL formulation should not be administered intravenously or using a continuous subcutaneous insulin infusion pump. This is endorsed, to avoid medication errors.

Absolute bioavailability of LY900014 following SC injection into the abdomen, deltoid, and thigh, was approximately 65%. Pharmacokinetics and glucodynamic effects are similar following SC injection into the abdomen and deltoid. Following SC injection into the thigh, the average Cmax was approximately 17% lower compared with injection into the abdomen, but the absorbed total amount was the same. The maximal glucose-lowering effect was observed slightly later following injection into the thigh compared with injection into the abdomen. It is known that the site of injection affects the absorption rate of insulins. In section 4.2 of the proposed SmPC, it is stated that LY900014 can be injected into the abdomen, upper arm, thigh or buttocks. Buttocks were not used as injection site in the clinical pharmacology program of LY900014. Buttocks may have been used for injection by patients in the Phase 3 studies, but no records thereof exist. However, considering the historical use of buttocks as an injection site for Humalog, the same injection sites can be approved for LY900014, since a cross-reference is added to section 5.2, reporting the absence of data for this injection site. As with other insulins, intravenous administration can be appropriate in hospital settings under special circumstances (e.g. during ketoacidosis).

Administration of LY900014 using a continuous subcutaneous insulin infusion (CSII) pump resulted in slightly faster absorption and slightly lower or comparable postprandial blood glucose levels compared with Humalog. The results support administration of LY900014 100 U/mL formulation using a CSII pump.

The pharmacokinetic results of euglycaemic clamp studies robustly support the conclusion that the absorption rate of insulin lispro following SC injection of LY900014 is increased compared with Humalog. The studies were conducted in presumably insulin-sensitive healthy subjects and in the target population of T1D and T2D patients, and very similar results were observed in each population. Left shifting of the concentration-time curve was constantly observed for LY900014 compared with Humalog. Statistically significant difference between LY900014 and Humalog was shown for pharmacokinetic parameters of early insulin exposure [AUC(0-15min), AUC(0-30min), AUC(0-1h), time to early half maximal drug concentration (early 50% t_{max}), and onset of appearance] in each study. Results of the meta-analysis indicated that approximately 8 times, 3 times, and 1.5 times more insulin lispro exposure was provided after SC injection of LY900014 than of Humalog for the first 15, 30 and 60 minutes, respectively. In the meta-analysis of studies in healthy subjects and T1D and T2D patients, the faster absorption was associated with a slightly higher C_{max} for LY900014 compared with Humalog (1.14-fold C_{max}; upper limit of 95% CI approximately 1.20). The slightly higher C_{max} is not expected to be clinically relevant for most subjects, although patients that are very insulin-sensitive might have increased risk for hypoglycaemia if they switch from Humalog to LY900014. This is addressed in section 4.4 of the proposed SmPC. Total insulin exposure [AUC(0-∞] was comparable following administration of LY900014 and Humalog, supporting the statement in section 4.2 of the SmPC that change from another mealtime insulin to LY900014 can be done on unit-to-unit basis. Late exposure to insulin lispro (e.g. AUC from 3h to end of PK sampling) was reduced for LY900014 compared with Humalog, which can be expected because the overall exposure was comparable and the early exposure was increased.

Likewise, the pharmacodynamic results of euglycaemic clamp studies robustly support the conclusion that the glucose-lowering effect of insulin lispro following SC injection of LY900014 takes place faster compared with Humalog, in line with the faster absorption of insulin lispro. Results of the meta-analysis demonstrated that the time of onset was approximately 10 minutes earlier and that approximately 3 times and 1.73 times more glucose was needed to be infused to maintain euglycaemia over the first 30 minutes and 60 minutes, respectively, following administration of LY900014 than of Humalog. Differences in other glucodynamic parameters were in line with the observed pharmacokinetic differences as well. The total glucose infused in the clamp was comparable between LY900014 and Humalog, maximum glucose infusion rate was approximately 12% higher for LY900014, and lower amount of glucose was needed to be infused to maintain euglycaemia in the late stage (after 3 to 4 hours after the start) of the clamp.

The effect of timing of the injection (immediately before the meal or 20 minutes after the start of the meal) on postprandial glucose excursion was investigated in patients with T1D and T2D using a standardised liquid mixed meal tolerance test. It was demonstrated in both patient groups at both injection times that the efficacy of LY900014 to control the postprandial increase of blood glucose was at least comparable with that of Humalog, and for some glucodynamic endpoints statistically significantly and clinically relevant better efficacy of LY900014 was observed. In addition, it was clearly demonstrated that the efficacy of both LY900014 and Humalog is better when they are injected before the meal compared with injection 20 minutes after the start of the meal. The SmPC states that "Liumjev is a mealtime insulin for subcutaneous injection and should be administered zero to two minutes before the start of the meal, with the option to administer up to 20 minutes after starting the meal (see section 5.1)". It is known that the efficacy of mealtime insulins is reduced if they are administered after the meal. It is acknowledged, however, that sometimes the patient cannot or simply forgets to administer the mealtime insulin before the meal. In such situations, it is preferable to administer the insulin after the start of the meal rather than not take mealtime insulin at all. The time limit of 20 minutes after starting a meal in the proposed SmPC has been investigated and is acceptable from clinical pharmacology perspective.

The absorption and the glucose-lowering effect following SC injection of LY900014 was similarly faster compared with Humalog in younger adults (18 to 45 years) and in elderly subjects (≥65 years).

Pharmacokinetic data in paediatric population is not yet available. The proposed therapeutic indication is for adults, and lack of paediatric data is sufficiently addressed in the product information.

After absorption of insulin lispro into the systemic circulation, the overall exposure (AUC0-∞) is comparable, and it is expected that distribution, elimination, and drug interactions are the same for LY900014 and Humalog. It was agreed in the scientific advice given by the CHMP in 2016 that, therefore, pharmacokinetic studies in subjects with impaired renal and hepatic function and drug-drug interaction studies would not be required for LY900014 and referring to studies conducted previously with Humalog is acceptable. The wording on subjects with impaired renal and hepatic function and drug interactions in the proposed product information is in line with the product information of Humalog, which is acceptable. To avoid any potential impact of local vasodilation by treprostinil on absorption of another insulin injected at the same time with LY900014, some wording has been added to the SmPC and PL to instruct patients to use a different injection site in these situations.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics and pharmacodynamics of LY900014 have been investigated in sufficient detail. Overall, the results of the clinical pharmacology studies support the conclusion that the absorption rate of insulin lispro following SC injection of LY900014 is increased compared with Humalog, which is associated with faster glucose-lowering effect.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose-finding studies were performed. The pharmacology program shows that even though the time-action curve is shifted left with LY900014 in comparison with Humalog, the overall glucose lowering effect of LY900014 is comparable to that of Humalog. Hence, overall, one unit of LY90000014 corresponds to one unit of Humalog.

2.5.2. Main studies

The efficacy data supporting this marketing authorization application are based on three pivotal Phase 3 studies:

- Two multiple daily injection studies: ITRM (T1D) and ITRN (T2D)
- A continuous subcutaneous insulin infusion study: ITSI (T1D)

A total of 421 healthy subjects and 342 patients with T1D or T2D were exposed to LY900014 in the 22 completed clinical pharmacology trials. Altogether 1944 patients with T1D or T2D received study drug (LY900014 or the active comparator Humalog) in the Phase 3 studies, of which 1165 received LY900014. The proportion of EU-patients in the Phase 3 studies were in the ITRM, 667/1316 (50.7%); in the ITRN, 234/750 (31.2%) and in ITSI 31/49 (63.3%).

The overall development plan including the three studies was accepted by the CHMP during scientific advice (EMA/CHMP/SAWP/400498/2016) to be sufficient for an indication in adults T1D and T2D subjects.

For the reader: Throughout the AR, %-units have been used for reporting HbA1c and mmol/L for glucose concentrations. If conversion between SI- and non-SI units for HbA1c and glucose concentration is needed, conversion tables can be found on the following websites:

https://www.diabetes.co.uk/downloads/HbA1c-units-conversion-chart.pdf

https://www.joslin.org/info/conversion_table_for_blood_glucose_monitoring.html

Methods

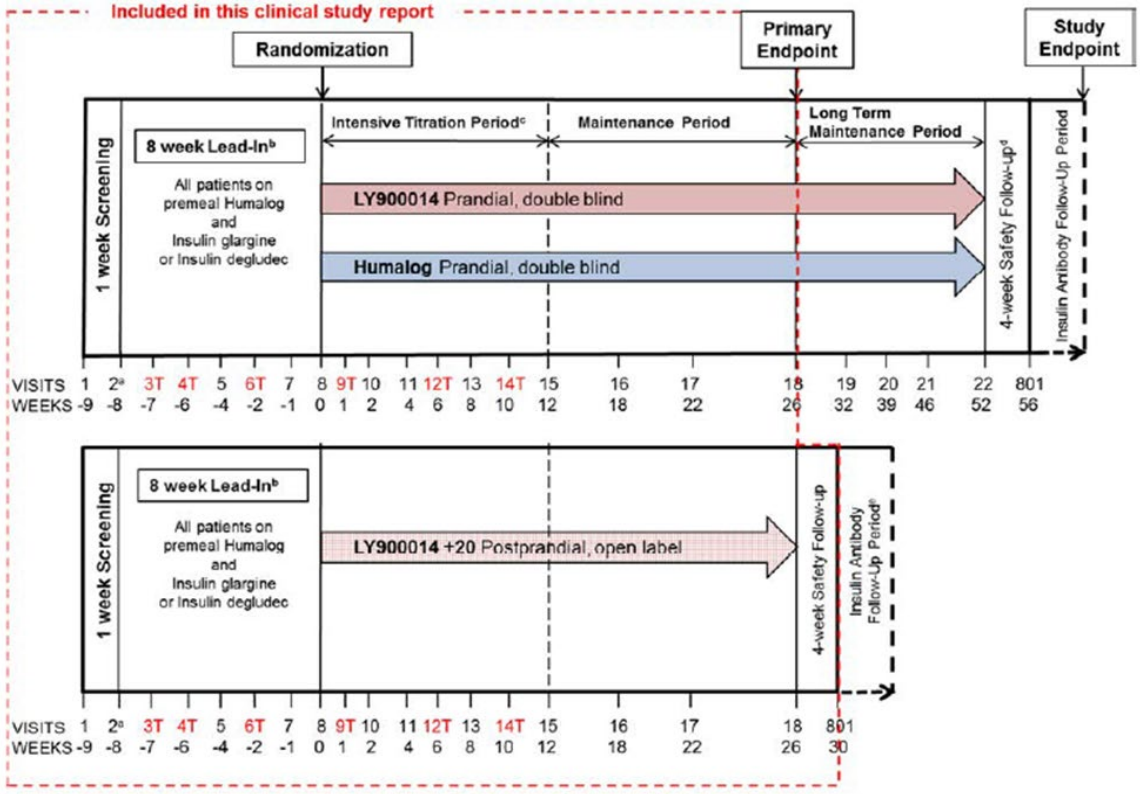
Studies ITRM and ITRN evaluated the safety and efficacy of LY900014 when administered as a prandial insulin as part of a multiple daily injection (MDI) regimen in adult patients with T1D and T2D, respectively. Studies ITRM and ITRN both included an 8-week lead-in period; a 12-week intensive titration period; and a 26-week controlled period assessing non-inferiority based on change in HbA1c of LY900014 compared with Humalog (primary objective).

ITRM was a Phase 3 prospective, randomized, outpatient, multinational, multicentre, 3-treatment group, parallel, active-controlled study conducted in patients with T1D currently using an MDI regimen. In 2 of the treatment groups, LY900014 and Humalog were administered immediately (0-2 minutes) prior to each meal in a double-blind manner. A third treatment group consisted of LY900014 administered 20 minutes after the start of a meal (LY900014+20) open-label, as it was not possible to blind this treatment group with different injection timing. (Figure 35).

In ITRM, patients in the 2 blinded treatment groups continued with double-blind treatment for an additional 26 weeks, for a total of 52 weeks. This was followed by a 4-week safety follow-up period. Patients who completed the 4-week safety follow-up visit (Visit 801) and had treatment-emergent

anti-insulin lispro antibodies that had not returned to prespecified baseline range (Visit 2) were asked to participate in follow-up to monitor antibody levels. The assessment of immunogenicity included analyses of treatment-emergent anti-insulin lispro antibody up to Visit 801 and analyses of anti-insulin lispro antibody return to baseline during the insulin lispro antibody safety follow-up period.

Figure 35. Study design, ITRM (T1DM)



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).

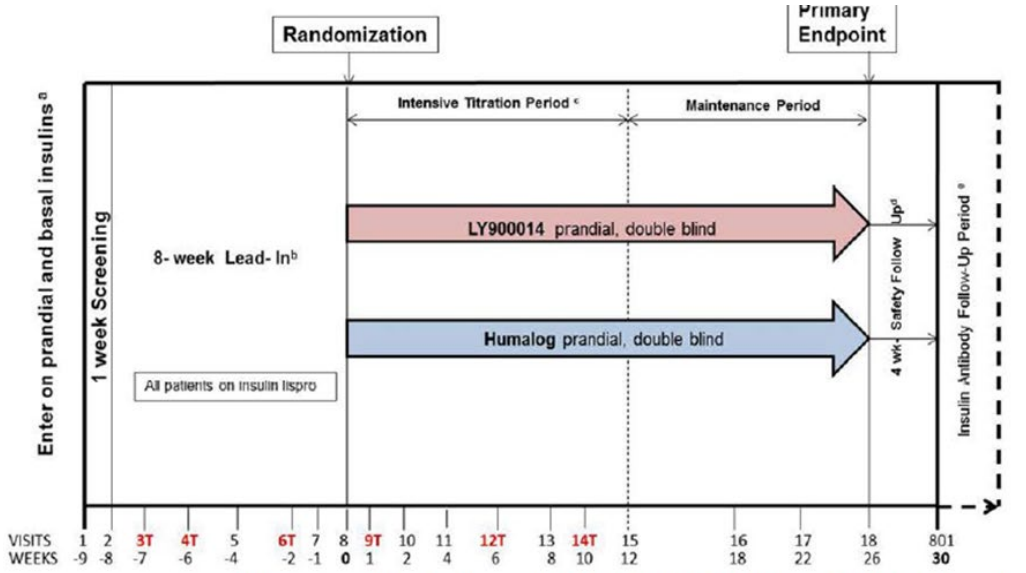
d Patients discontinued study insulins at Week 26 for the LY900014+20 open-label treatment group or will discontinue study insulins at Week 52 for the 2 blinded treatment groups and the LY900014 open-label treatment group in Japan.

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.

An Addendum (ITRM CGM substudy) to the study compared LY900014 and Humalog with respect to the incremental $AUC_{0\text{-}2hours}$ after breakfast obtained from up to 14 days of CGM use at Week 26. Blinded CGM was planned to be offered to a subgroup of up to 315 patients (105 per treatment group) at selected sites in Study ITRM.

ITRN was a Phase 3, prospective, double-blind, randomized, outpatient, multinational, multicenter, 2-group, parallel, active-controlled study conducted in patients with T2D currently treated with basal insulin in combination with at least 1 prandial insulin injection or premixed insulin with at least 2 injections daily (figure 36)

Figure 36. Study design, ITRN (T2D)



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.

Study ITRM (T1D) was stratified by country, HbA1c at entry, type of basal insulin during the lead-in period, and prandial insulin dosing plan at randomization. Study ITRN was stratified by country, HbA1c at entry, type of basal insulin during the lead-in period, and number of prandial insulin doses at entry.

At Week 0 after completion of the MMTT, patients in:

- Study ITRM were randomized (4:4:3) to either LY900014 (blinded) at mealtime or Humalog (blinded) at mealtime, or LY900014+20 (open-label) post-meal
- Study ITRN were randomized (1:1) to either LY900014 (blinded) at mealtime or Humalog (blinded) at mealtime.

A treat-to-target approach to diabetes management was implemented in both studies. The protocols provided prespecified glycaemic targets and recommended basal and prandial insulin dose algorithms for guidance. The prescribed basal and prandial insulin dose was however determined by, and the responsibility of the investigator. The treat-to-target approach was used in 3 different periods:

- basal insulin titration during the 8-week lead-in period (optimization of basal insulin)
- prandial insulin titration during the 12-week intensive titration period
- basal and prandial insulin adjustments during the 14-week maintenance period to address hypoglycaemia or unacceptable hyperglycaemia.

Prandial insulin was individually determined by either:

- Pattern adjustment: The patient was prescribed a fixed dose or dose range of insulin for each meal. The fixed dose or dose range of insulin may have been individualized for each meal.

  or

- Carbohydrate counting: If the patient performed carbohydrate counting for prandial insulin dosing (insulin-to-carbohydrate ratio plan) prior to study enrolment, this plan may have been continued during the study. The prandial insulin dose was based on the patient estimated carbohydrate content of the meal (as unit insulin per grams carbohydrate).

Protocol deviations occurred in 9.2% (112/1222) of patients in the ITRM (T1D) and 16.2% (109/673) in the ITRN. As the deviations were scattered across the three study arms, they are not considered to have relevant effect on the results of the analyses.

Table 10 presents key inclusion and exclusion criteria, study treatments, glycaemic targets, stratification factors and participating countries for studies ITRM and ITRN. ITRM was conducted at 166 study centres in 18 countries, and ITRN at 131 study centres in 15 countries.

Table 10. Phase 3 MDI studies in T1D (ITRM) and T2D (ITRN)

Study ITRM	Study ITRN
Design Element	
Key Inclusion	
HbA1c 7.0% to 9.5%. BMI ≤ 35 kg/m^2 Prior basal insulin for at least 30 days prior to screening: • Insulin glargine 100 units/mL, once or twice daily • Insulin glargine 300 units/mL, once daily • Insulin detemir 100 units/mL, once or twice daily • Insulin degludec 100 units/mL or 200 units/mL, once daily • Neutral Protamine Hagedorn (NPH), once or twice daily Prior prandial insulin for at least 90 days prior to screening: • Insulin lispro • Insulin aspart • Insulin glulisine	HbA1c 7.0% to 10.0%. BMI ≤ 45 kg/m^2 Prior basal insulin for at least 90 days prior to screening: • Insulin glargine 100 units/mL • Insulin glargine 300 units/mL • Insulin detemir 100 units/mL • Insulin degludec 100 units/mL or 200 units/mL • Neutral Protamine Hagedorn (NPH) At least 1 prandial insulin injection for at least 90 days prior to screening: • Insulin lispro, or • Insulin aspart, or • Insulin glulisine, or • Regular insulin or At least 2 daily injections • premixed analog or human insulin regimens with any basal and prandial insulin combination Prior use of up to 3 OAMs at stable doses at least 90 days prior to screening and in accordance with local regulations • Metformin [a] • Dipeptidyl peptidase-4 (DPP-4) inhibitor • Sodium glucose cotransporter 2 (SGLT2) inhibitor [a] • Sulfonylurea • Meglitinide • Alpha-glucoside inhibitor

Table 11. Phase 3 MDI studies in T1D (ITRM) and T2D (ITRN) (continued)

Study ITRM	Study ITRN
Design Element	
Key Exclusion	
• Use of regular human insulin, premixed insulin, insulin human inhalation powder, CSII, OAMs or injectables other than insulin within 90 days prior to screening • Excessive resistance to insulin (total insulin dose >1.5 U/kg) • More than 1 episode of severe hypoglycemia in prior 6 months • More than 1 episode requiring ER/hospitalization for severe hyperglycemia/diabetic ketoacidosis in prior 6 months	• Use of insulin human inhalation powder, CSII, thiazolidinediones, GLP-1 receptor agonist, or pramlintide within 90 days prior to screening • Excessive resistance to insulin (total insulin dose >2.0 U/kg) • Any episode of severe hypoglycemia in prior 6 months • One or more episode of diabetic ketoacidosis or hyperglycemic hyperosmolar state in prior 6 months
Basal insulin during Study	
Insulin glargine 100 units/mL, once or twice daily Insulin degludec 100 units/mL, once daily	Insulin glargine 100 units/mL, once or twice daily Insulin degludec 100 units/mL or 200 units/mL, once daily
Blood Glucose Targets and Ranges	
Pre meals: Target: 100 mg/dL (5.6 mmol/L) Range: 80 to <110 mg/dL (4.4 to 6.1 mmol/L) Pre bedtime: Range: 90 to 130 mg/dL (5.0 to 7.2 mmol/L) 1-2 hour postprandial: Target: <140 mg/dL (7.8 mmol/L)	
Stratification Factors	
• Country • HbA1c stratum (≤7.5%, >7.5%) • type of basal insulin during the lead-in period (glargine 100 U/mL or degludec 100U/mL) • prandial insulin dosing plan at randomization (carbohydrate counting, pattern adjustment)	• Country • HbA1c stratum (≤8.0%, >8.0%) • type of basal insulin during the lead-in period (glargine 100 U/mL or degludec [100 U/mL or 200 U/mL]) • number of prandial doses at study entry (<3, ≥3)
Participating countries	
Puerto Rico[b,c], US[b,c], Japan, Taiwan, Austria, Germany[c], Greece, Italy[c], Poland[c], Romania, Russia, Slovakia, Spain[c], Sweden, Argentina, Australia[c],India, Mexico[c], New Zealand[c].	Puerto Rico[b], US[b], Japan, South Korea, Taiwan, Czech Republic, Germany, Hungary, Italy[d], Russia, Slovakia, Spain[d], Argentina, Australia, India, Mexico.

Phase 3 MDI Studies Supporting the Efficacy of LY900014 in Patients with Type 1 and Type 2 Diabetes

Abbreviations: BMI = body mass index; CSII = continuous subcutaneous insulin infusion; CGM = continuous glucose monitoring; GLP-1 = glucagon-like peptide 1; HbA1c = hemoglobin A1c; MDI = multiple daily injections; OAM =- oral antidiabetic medication.

[a] Metformin and/or SGLT2 could be continued throughout Study ITRN

[b] Puerto Rico and US were pooled for analysis in Studies ITRM and ITRN

[c] Countries that participated in the CGM addendum

[d] Italy and Spain were pooled for analysis in Study ITRN

Mixed-meal tolerance test (MMTT)

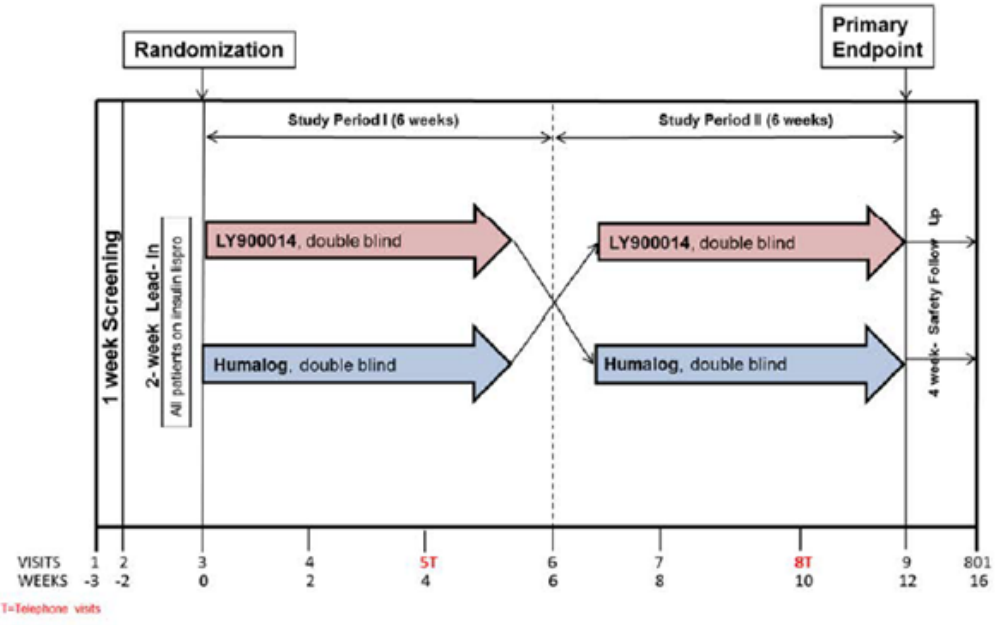
In both studies, patients were to arrive at the investigative site with a fasting BG in the range of 3.9 to 10.0 mmol/L). Insulin doses used during the MMTT were individualized based on a patient's ICR or dosing recommendations provided in the protocol. Patients were asked to:

- inject basal insulin according to their usual schedule
- avoid major changes in dietary intake or physical activity during the 3 days
- avoid administering correction doses with study insulins within 4 hours prior of the start of the MMTT
- consume the liquid test meal (~100 grams of carbohydrate and ~700 kcal) within 15 minutes

ITSI was a 2-treatment, 2-period (6-week treatment each) crossover design trial that evaluated the safety and compatibility of LY900014 in the treatment of patients with T1D when administered via CSII. The study was designed to compare LY900014 and Humalog with respect to the rate (events/patient/30 days) of infusion set failures that led to premature infusion set changes due to a pump occlusion alarm OR due to unexplained hyperglycaemia with blood glucose (SMBG >13.9 mmol/L) that did not decrease within 1 hour following a correction bolus delivered via the pump. The study included a 1-week screening period and a 2-week lead-in period followed by a 2-period crossover and a 4-week post-treatment safety follow-up. Each period of the crossover consisted of 6 weeks of treatment with no washout between periods (Figure 37).

Patients currently treated with a rapid-acting insulin analogue via CSII were eligible for inclusion in the trial. All patients were transferred to Humalog at Visit 2 so that all patients were using Humalog during the lead-in period. Patients were required to have been using the MiniMed 530G, MiniMed 630G (US) or 640G (EU) insulin pump. The bolus delivery speed for all pumps was set to standard speed (1.5 U/minute) for the duration of the lead-in and treatment phases of the study. The purpose of the lead-in period (prior to randomization) was to obtain preliminary diagnostic tests, determine baseline hypoglycaemia rate, and evaluate pump basal rates and bolus calculator settings (carbohydrate ratio [CR], insulin sensitivity factor [ISF], and active insulin time [AIT] for calculating mealtime and correction bolus doses) for appropriateness.

Figure 37. Study design, ITSI (T1D)



Study Participants

Please refer to the information presented in the section below (Treatments).

Treatments

ITRM (T1D) and ITRN (T2D)

Basal insulin options were limited to insulin glargine (once or twice daily) or insulin degludec. Patients were asked to maintain basal insulin dose timing and frequency throughout the study.

Mealtime insulin: All patients using insulin aspart, insulin glulisine, regular insulin, or premixed insulin were transferred to Humalog at Visit 2 (screening) so that all patients were receiving Humalog throughout the lead-in period. At visit 8, patients were randomized to either preprandial LY900014 or preprandial Humalog at each meal in both ITRM and ITRN. ITRM also contained a third arm, open-label, with postprandially injected LY900014 up to Week 26. During the long-term maintenance period (weeks from 26 to 52) of ITRM, only the double-blind arms of ITRM were continued (except in Japan, where the treatment period ended after 52 weeks). (Figures 3.3.5.1 and 3.3.5.2, Tables 3.3.1 and 3.3.5.1)

Study medication: Study insulins (LY900014 and Humalog) were provided in blinded prefilled pens containing a concentration of 100 U/mL in 3-mL cartridges of either LY900014 or Humalog. The open-label prefilled pens in ITRM contained a concentration of 100 U/mL of LY900014. In both ITRM and

ITRN, LY900014 and Humalog was injected 0-2 minutes prior to meal. In ITRM, the postprandial injection of LY900014 was instructed to be injected 20 minutes post-meal.

ITSI (T1D, CSII)

All patients were transferred from their pre-trial prandial insulin to use Humalog during the lead-in period**.** Dexcom G5 was used by all patients in real-time mode beginning at Visit 2 and continuing throughout the treatment phase of the study. At Visit 3 (Randomization Visit), patients were randomly assigned to 1 of the 2 treatment sequences of double-blind LY900014 and Humalog. During the study, patients were expected to use the pump's bolus calculator to determine mealtime and correction bolus doses.

Objectives

The efficacy objectives of ITRM and ITRN are presented in table 12, and of ITSI, in table 13.

Table 12. Efficacy objectives of ITRM (T1D) and ITRN (T2D)

ITRM (MDI; T1D)	ITRN (MDI;T2D)
Primary Objective	
To test the hypothesis that LY900014 was noninferior to Humalog on glycemic control (NIM=0.4% for HbA1c) in patients with diabetes, when administered as prandial insulin (0-2 minutes prior to the meal), in combination with basal insulin for 26 weeks. Note: The primary endpoint was also assessed using a NIM of 0.3% to meet criteria required by CHMP.	
Multiplicity Adjusted Objectives	
To test the hypothesis that change in HbA1c at 26 weeks with LY900014+20 was noninferior to Humalog (NIM=0.4%, 0.3%) To test the hypothesis that LY900014 was superior to Humalog at Week 26: • in controlling 1-hour PPG excursions • in controlling 2-hour PPG excursions • on improving glycemic control (HbA1c)	To test the hypothesis that LY900014 was superior to Humalog at Week 26: • in controlling 1-hour PPG excursions • in controlling 2-hour PPG excursions • on improving glycemic control (HbA1c)
Other Key Secondary or Exploratory Objectives / Endpoints	
To compare LY900014, LY900014+20 and Humalog with respect to: • 1,5-Anhydroglucitol values • 10-point SMBG measurements; within and between day variability • total, basal, and prandial insulin dose • percentage of patients achieving HbA1c <7.0% and ≤6.5% • percentage of patients achieving HbA1c targets of <8.0%, ≤9.0% and >9.0%	
ITRM CGM Substudy Objectives	
To compare LY900014, LY900014+20 and Humalog after 14 days of blinded CGM use with respect to: • the incremental AUCs after breakfast and all meals combined • the duration of time glucose values are within target range (71 and 140 mg/dL [3.9 and 7.8 mmol/L]), (71 and 180 mg/dL [3.9 and 10.0 mmol/L]) • ambulatory glucose profiles • glycemic variability	

Abbreviations: AUC = area under the concentration versus time curve; CHMP = Committee for Medicinal Products for Human Use; HbA1c = hemoglobin A1c; MDI = multiple daily injections; NIM = noninferiority margin; PPG = postprandial glucose; T1D = type 1 diabetes; T2D = type 2 diabetes.

Table 13. Efficacy objectives of of ITSI (T1D, CSII)

Secondary Objectives
To compare LY900014 and Humalog with respect to: • total, basal, and bolus insulin dose • the interstitial glucose reduction rate from hyperglycemia following a non-meal-related correction bolus delivered via the pump
Exploratory Objectives
To compare LY900014 and Humalog with respect to: • the incremental AUCs after breakfast, obtained from CGM use • the duration of time glucose values are within target range (71 and 180 mg/dL [3.9 and 10.0 mmol/L]), obtained from CGM use • the duration of time glucose values are within target range (71 and 140 mg/dL [3.9 and 7.8 mmol/L]), obtained from CGM use • the glucose profiles, obtained from CGM use • the glucose variability, obtained from CGM use • HbA1c • 1,5-Anhydroglucitol values

Abbreviations: AUC = area under the concentration versus time curve; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c.

Outcomes/endpoints

The outcomes/ endpoints are given in the section above on Objectives.

Sample size

In ITRM and ITRN, following assumptions for the primary endpoint, the change from baseline to 26 weeks in HbA1c, were made in the sample size calculations: a NIM of 0.4%, no true difference between treatment arms, a SD of 1.1%, and a 15% dropout rate for 26 weeks.

In ITRM 371 completers were aimed in each double-blind treatment group, and in ITRN 284 completers in each group. This leads to at least 99% power to show non-inferiority between LY900014 and Humalog. If a lower NIM 0.3% was used, in ITRM 95% power was reached and in ITRN 90%.

In ITRM with 4:4:3 randomization ratio (LY900014, Humalog, and LY900014+20), approximately 1199 patients needed to be randomized, and in ITRN approximately 670 patients needed to be randomized.

The ITSI study did not state any statistical hypothesis, and thus was not statistically powered.

Randomisation

Patients who met all criteria for enrollment were randomized to double-blind treatment at Visit 8 in ITRM and ITRN.

In **ITRM** patients were randomized to double-blind LY900014, double-blind Humalog, or open-label LY900014+20 in a 4:4:3 ratio. Stratification was by country, HbA1c stratum (≤7.5%, >7.5% at Visit 7), type of basal insulin during the lead-in period (glargine U-100 or degludec U-100), and prandial insulin dosing plan at randomization (carbohydrate counting, pattern adjustment).

In **ITRN** patients were randomized to 1 of the 2 treatment groups in 1:1 ratio (double-blind LY900014 administered at mealtime or double-blind Humalog administered at mealtime). Stratification was by

country, HbA1c stratum (≤8.0%, >8.0% at Visit 7), type of basal insulin received during the lead-in period (insulin glargine U-100 or insulin degludec [U-100 or U-200]), and number of prandial doses at study entry (<3, ≥3).

In ITSI, patients who completed the lead-in period were randomized to double-blind treatment at Visit 3. Patients were randomized to 1 of the 2 treatment sequences in a 1:1 ratio: Sequence A: LY900014 → Humalog or Sequence B: Humalog → LY900014.

Stratification was by region (US, outside of the US [OUS]), historical use of SmartGuard/Threshold Suspend (Yes, No), and HbA1c stratum (≤7.3%, >7.3% at Visit 1).

Assignment to treatment groups (Studies ITRM and ITRN) or treatment sequences (Study ITSI) was performed as a permuted block randomisation within each combination of stratification factors.

Blinding (masking)

In ITRM and ITRN, the treatment groups, LY900014 and Humalog, were administered immediately (0-2 minutes) prior to each meal in a double-blind manner. The blinded prefilled pens contained a concentration of 100 U/mL in 3-mL cartridges of either LY900014 or Humalog. Investigators, patients, and study site personnel were blinded to assigned dosing regimens, throughout the study. A third open-label treatment group in **ITRM** consisted of LY900014 administered 20 minutes after the start of a meal (LY900014+20).

In **ITSI** study both treatment groups, LY900014 and Humalog, had basal rates and bolus doses given via CSII. Investigators, patients, and study site personnel were blinded to assigned dosing regimens throughout the study.

To preserve the blinding of the studies, the Applicant study teams were blinded to double-blind treatment assignments until after the primary endpoint database lock, and no changes were made to the database after unblinding.

Statistical methods

In all studies, the primary patient population was called *randomized* and defined as all patients who were randomly assigned to study treatment or treatment sequence. Treatment group was defined on the basis of the randomization.

In ITRM and ITRN the analyses for the primary and multiplicity adjusted objectives were performed for the *intention-to-treat (ITT) estimand* (including all data collected through Week 26, regardless of IP use) and the *efficacy estimand* (including data collected prior to discontinuation of IP through Week 26).

For the analysis of HbA1c using the *ITT estimand*, imputation of missing data at week 26 utilized the patient-level observed baseline value plus noise. For the *efficacy estimand*, missing data were addressed by using a mixed-effect model repeated measures (MMRM) analysis for continuous longitudinal variables. The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c included the fixed class effects of treatment, strata (pooled country, type of basal insulin, and number of prandial doses at study entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value.

An ANCOVA model with strata and treatment as fixed effects and baseline as a covariate was used to analyze the 1-hour and 2-hour PPG excursions for both the *efficacy* and *ITT estimands*. As the PPG excursions were only measured twice: at baseline and week 26, the subjects who did not have data either at baseline or at week 26 were excluded from the analysis, and as a consequence the estimated treatment

effect for *ITT estimand* was rather *efficacy estimand* than ITT, which is eventually deemed to be negligible as far as the treatment effect was concerned.

The applicant conducted several pre-planned subgroup analysis for the primary endpoint using the *efficacy estimand*.

As there were no hypothesis stated in ITSI trial, all statistical analyses are descriptive in nature.

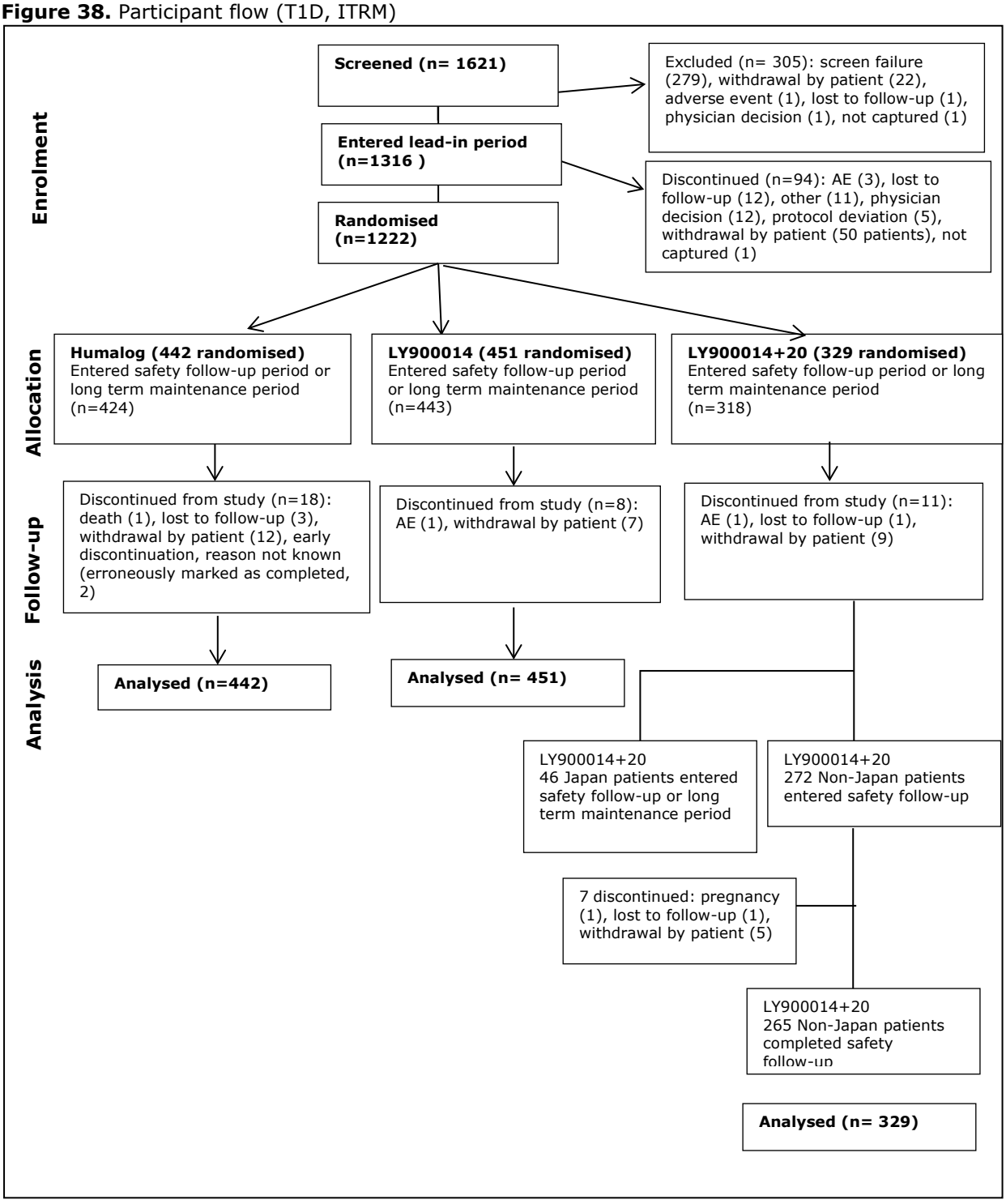
Results

Participant flow

ITRM (T1D)

The disposition of study subjects in ITRM (T1D) is presented in figure 38:

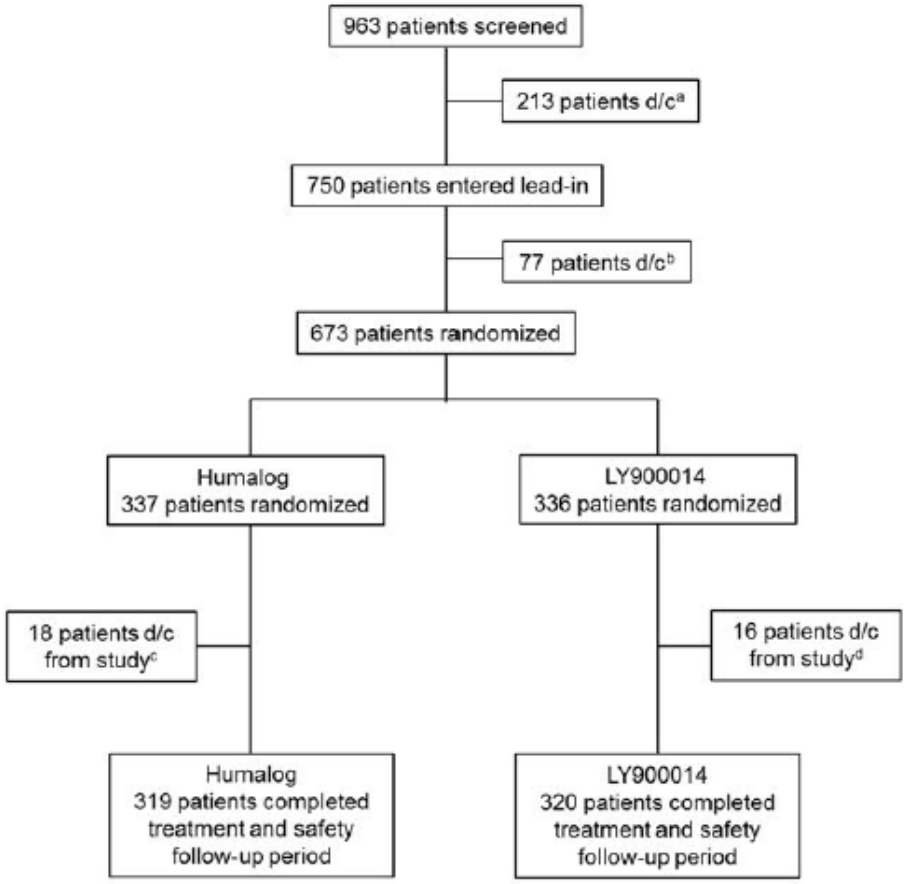
Figure 38. Participant flow (T1D, ITRM)



ITRN (T2D)

Out of 963 screened patients, 337 were randomised to receive Humalog and 336 to receive LY900014 (Figure 39

Figure 39. Patient disposition ITRN



Abbreviation: d/c=discontinued.

a Reasons for discontinuation: screen failure (189 patients), withdrawal by patient (21 patients), lost to follow-up (3 patients).

b Reasons for discontinuation: adverse event (3 patients), lost to follow-up (4 patients), other (20 patients), physician decision (6 patients), protocol deviation (3 patients), withdrawal by patient (41 patients).

c Reasons for discontinuation: adverse event (1 patient), death (1 patient), lost to follow-up (6 patients), withdrawal by patient (10 patients).

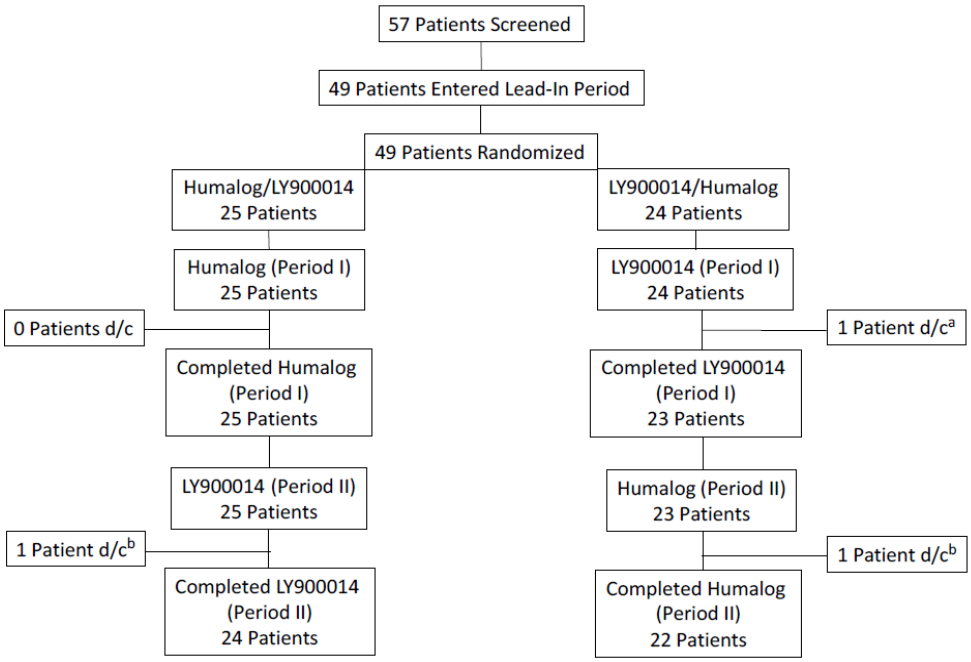
d Reasons for discontinuation: adverse event (1 patient), death (2 patients), lost to follow-up (3 patients) other (2 patients), withdrawal by patient (8 patients).

A total of 34 patients (Humalog, 18 patients [5.3%]; LY900014, 16 patients [4.8%]) discontinued the study early during the randomization to safety follow-up period. The most common reason for study discontinuation in each group was withdrawal by subject. There were no statistically significant treatment differences in number of patients discontinued or in the reasons for discontinuation. The death in the Humalog treatment group was reported as study discontinuation due to death and treatment discontinuation due to an AE (sudden death). The 2 deaths in the LY900014 group were reported as study and treatment discontinuation due to death.

ITSI

The disposition of study subjects in ITSI is presented in figure 40:

Figure 40. Patient disposition during the 12-week treatment period - ITSI



[a] Reasons for discontinuation: protocol violation.
[b] Reasons for discontinuation: withdrawal by patient.
Note: One patient in sequence Humalog/LY900014 discontinued from the study at Visit 9 (Week 12) after completing Period II.
Sources: /lillyce/prd/ly900014/i8b_mc_itsi/final/output/shared/tfl/smdis01.rtf; smdis02.rtf; smdis03.rtf.

Recruitment

ITRN: First patient visit occurred on 14 July 2017 and first patient was randomised on 19 September 2017. Of a total of 750 patients entered to the study, 234 were from the EU (Czech Republic, Germany, Hungary, Italy, Slovakia, and Spain). The non-EU sites were situated in the US, Argentina, Australia, India, Japan, South Korea, Mexico, Russia, and Taiwan.

ITRM: First patient's visit for ITRM and for the CGM Addendum occurred on 17 July 2017 and first patient was randomised on 12 September 2017 for both. Altogether 667/1316 patients were entered from the EU (Austria, Germany, Greece, Italy, Poland, Romania, Slovakia, Spain, and Sweden); the non-EU sites were situated in the US, Argentina, Australia, India, Japan, Russia, and Taiwan.

ITSI: Five principal investigators (endocrinologists specializing in diabetes) conducted the study: three in the US (26 entered patients) and two in Spain (31 entered patients). First patient visit occurred on 21 February 2018; first patient was randomised on 14 March 2018.

Conduct of the study

The overall conduct of the studies is acceptable. Protocol deviations were not deemed to have affected study results.

Baseline data

Baseline demographic, disease and treatment characteristics by treatment group for studies ITRM(T1D) and ITRN (T2D) are presented in Table 14. No statistically significant differences in key demographic features or baseline characteristics were observed between treatment groups in studies ITRM (T1D) and ITRN (T2D).

Table 14. Baseline characteristics and stratification factors in MDI studies: ITRM (T1D) and ITRN (T2D)

	Study ITRM (T1D) N=1222			Study ITRN (T2D) N=673	
Variable Statistic	**Humalog N=442**	**LY900014 N=451**	**LY900014+20 N=329**	**Humalog N=337**	**LY900014 N=336**
Gender (n [%])					
Female	186 (42.1)	201 (44.6)	147 (44.7)	162 (48)	152 (45)
Male	256 (57.9)	250 (55.4)	182 (55.3)	175 (52)	184 (55)
Age (years)					
Mean (SD)	44.5 (13.6)	44.1 (13.7)	44.5 (14.3)	61.0 (9.2)	60.2 (9.4)
Age Group (n [%])					
18 to <65 years	407 (92.1)	415 (92.0)	302 (91.8)	194 (57.6)	212 (63.1)
≥65 to <85 years	35 (7.9)	36 (8.0)	27 (8.2)	143 (42.4)	124 (36.9)
Race; (n [%])					
Asian	78 (17.6)	86 (19.1)	63 (19.1)	81 (24.0)	83 (24.7)
Black or African American	9 (2.0)	7 (1.6)	5 (1.5)	16 (4.7)	14 (4.2)
White	344 (77.8)	346 (76.7)	254 (77.2)	229 (68.0)	233 (69.3)
Ethnicity					
Hispanic or Latino	33 (7.5)	35 (7.8)	35 (10.6)	78 (23.1)	79 (23.5)
Not Hispanic or Latino	397 (89.8)	399 (88.5)	283 (86.0)	208 (61.7)	214 (63.7)
Duration of Diabetes (years)					
Mean (SD)	19.1 (12.0)	18.8 (12.3)	18.8 (11.7)	16.6 (7.9)	16.4 (7.8)
BMI (kg/m^2)					
Mean (SD)	26.4 (4.3)	26.6 (4.2)	26.7 (4.6)	32.4 (5.8)	32.1 (5.7)
HbA1c Mean (SD)					
Study Entry (%)	8.02 (0.67)	8.04 (0.65)	8.03 (0.61)	8.30 (0.75)	8.30 (0.79)
Study Entry (mmol/mol)	64.17 (7.31)	64.40 (7.05)	64.24 (6.71)	67.17 (8.25)	67.17 (8.63)
Baseline (%)	7.33 (0.67)	7.34 (0.65)	7.36 (0.64)	7.31 (0.72)	7.27 (0.68)
Baseline (mmol/mol)	56.65 (7.27)	56.68 (7.08)	56.94 (7.00)	56.42 (7.92)	55.98 (7.45)
Fasting Glucose Mean (SD)					
Visit 2 (mg/dL)	176.05 (72.53)	171.61 (75.29)	175.00 (75.25)	163.77 (55.84)	160.57 (56.32)
Visit 2 (mmol/L)	9.77 (4.03)	9.53 (4.18)	9.71 (4.18)	9.09 (3.10)	8.91 (3.13)
Baseline (mg/dL)	126.19 (41.56)	126.29 (41.98)	129.51 (44.67)	123.43 (36.86)	123.31 (33.38)
Baseline (mmol/L)	7.01 (2.31)	7.01 (2.33)	7.19 (2.48)	6.85 (2.05)	6.85 (1.85)

Table 15. Baseline characteristics and stratification factors in MDI studies: ITRM (T1D) and ITRN (T2D) (continued)

	Study ITRM (T1D) N=1222			Study ITRN (T2D) N=673	
Variable Statistic	**Humalog N=442**	**LY900014 N=451**	**LY900014+20 N=329**	**Humalog N=337**	**LY900014 N=336**
Stratification Factors					
Prandial Insulin Dosing Plan					
Carbohydrate Counting	205 (46.4)	201 (44.6)	148 (45.0)	30 (8.9)	24 (7.1)
Pattern adjustment	237 (53.6)	250 (55.4)	181 (55.0)	307 (91.1)	312 (92.9)
Number of Prandial Doses at Study Entry					
<3 per day				85 (25.2)	83 (24.7)
≥3 per day				252 (74.8)	253 (75.3)
Type of Basal Insulin at Baseline					
Insulin glargine	249 (56.3)	254 (56.3)	180 (54.7)	257 (76.3)	260 (77.4)
Insulin degludec	193 (43.7)	197 (43.7)	149 (45.3)	80 (23.7)	76 (22.6)
HbA1c Group (n [%]) at Baseline					
≤8.0%				291 (86.4)	286 (85.1)
>8.0%				46 (13.6)	50 (14.9)
>7.5%	154 (34.8)	156 (34.6)	107 (32.5)		
≤7.5%	288 (65.2)	294 (65.2)	215 (65.3)		
Personal CGM/FGM Use, n (%)					
Yes	51 (11.5)	45 (10.0)	46 (14.0)		

Abbreviations: BMI = body mass index; CGM = continuous glucose monitoring; FGM = flash glucose monitoring; HbA1c = hemoglobin A1c; N = number of subjects in the analysis population; n = number of subjects in the specified category; SD = standard deviation; T1D = type 1 diabetes; T2D = type 2 diabetes.

Study ITSI was smaller (n= 49), and not powered to show statistical difference in efficacy between study arms. As expectable for a small study, some differences in characteristics between study arms are seen, which however are not regarded as relevant for interpretation of the obtained results (Table 16).

Table 16. Baseline characteristics and stratification factors in ITSI (T1D,CSII)

Variable Statistic	Study ITSI (T1D) N=49	
	Humalog/LY900014 N=25	LY900014/Humalog N=24
Gender (n [%])		
Female	14 (56.0)	12 (50.0)
Male	11 (44.0)	12 (50.0)
Age (years)		
Mean (SD)	36.72 (10.37)	42.50 (12.47)
Age Group (n [%])		
<40 years	16 (64.0)	10 (41.7)
≥40 years	9 (36.0)	14 (58.3)
Race; (n [%])[a]		
Black or African American	0 (0.0)	1 (4.2)
White	25 (100.0)	23 (95.8)
Ethnicity		
Not Hispanic or Latino	25 (100.0)	23 (95.8)
Duration of Diabetes (years)		
Mean (SD)	20.83 (9.20)	21.77 (14.64)
Duration of CSII Use (years)		
Mean (SD)	9.62 (6.74)	7.81 (5.99)
Body Weight (kg)		
Mean (SD)	79.22 (17.04)	74.47 (11.78)
BMI (kg/m^2)		
Mean (SD)	26.96 (3.97)	26.76 (3.60)
HbA1c (%) Mean (SD)		
Study Entry	7.34 (0.66)	7.11 (0.76)
Baseline	7.17 (0.68)	6.95 (0.68)
Stratification Factors		
HbA1c Group (n [%]) at Baseline		
>7.3%	10 (40.0)	6 (25.0)
≤7.3%	15 (60.0)	18 (75.0))
Historical Use of SmartGuard/ Threshold Suspend		
Yes	5 (20.0)	5 (20.8)
No	20 (80.0)	19 (79.2)
Pooled Country		
United States	11 (44.0)	10 (41.7)
Spain	14 (56.0)	14 (58.3)

Abbreviations: BMI = body mass index; CSII = continuous subcutaneous insulin infusion; N = number of patients in the analysis population; n = number of patients in the specified category; SD = standard deviation; T1D = type 1 diabetes.

Numbers analysed

Efficacy analyses were conducted for all randomized patients according to treatment assignment. The analyses for the primary and multiplicity adjusted objectives were performed for the efficacy estimand (including data collected prior to permanent discontinuation of IP) and for the ITT estimand (including all data collected, regardless of IP use).

Compliance of the timing of prandial insulin administration relative to time of meal in study ITRM was not optimal, especially for post-meal dosing. When all postbaseline visits for the morning meal were included, the respective proportions were as follows: LY900014, n=179 (90.9%); Humalog, n=174 (84.1%);

LY900014+20, n=96 (64.9%). At Week 26, as well as for the overall mean at the midday and evening meals, the proportions of patients with average dose times within the protocol-specified time window were similar to the proportions at the morning meal. The mean dosing time in LY900014+20 group was 15.3-15.4 minutes, depending on meal (morning, midday, evening). However, it is assuring for interpretation of study results that the median administration time in the LY900014+20 group was between 19.2 to 19.4 minutes; hence, most patients injected the insulin according to protocol.

Outcomes and estimation

The summary of efficacy endpoint for ITRM (T1D) and ITRN (T2D) is shown for the efficacy estimand results (table 17).

Table 17. Summary of Primary and Multiplicity Adjusted Efficacy Results for Phase 3 MDI Studies Using the Graphical Approach (Efficacy Estimand) (in mmol/mol and mmol/L)

Hypothesis	Test	LSM (SE)		LY-Humalog LSM Diff (95% CI)	p-Value	NIM	Objective Met?
		Humalog	LY900014				
ITRM							
(H1) Change in HbA1c (mmol/mol)	NI	-0.6 (0.34)	-1.4 (0.33)	-0.8 (-1.7, 0.0)		4.4, 3.3	**Yes**
		Humalog	**LY900014+20**				
(H5) Change in HbA1c (mmol/mol)	NI	-0.6 (0.34)	0.8 (0.39)	1.4 (0.5, 2.4)		4.4, 3.3	**Yes**
		Humalog	**LY900014**				
(H2) 1 hr PPG excursion (mmol/L)	SP	4.13 (0.185)	2.57 (0.185)	-1.55 (-1.96, -1.14)	<0.001		**Yes**
(H3) 2 hr PPG excursion (mmol/L)	SP	5.77 (0.250)	4.04 (0.250)	-1.73 (-2.28, -1.18)	<0.001		**Yes**
(H4) Change in HbA1c (mmol/mol)	SP	-0.6 (0.34)	-1.4 (0.33)	-0.8 (-1.7, 0.0)	0.060		**No**
ITRN							
(H1) Change in HbA1c (mmol/mol)	NI	-4.7 (0.46)	-4.1 (0.46)	0.6 (-0.6, 1.8)		4.4, 3.3	**Yes**
(H2) Change 1 hr PPG excursion (mmol/L)	SP	4.16 (0.20)	3.50 (0.20)	-0.66 (-1.01, -0.30)	<0.001		**Yes**
(H3) Change 2 hr PPG excursion (mmol/L)	SP	5.43 (0.25)	4.47 (0.25)	-0.96 (-1.41, -0.52)	<0.001		**Yes**
(H4) Change in HbA1c (mmol/mol)	SP	-4.7 (0.46)	-4.1 (0.46)	0.6 (-0.6, 1.8)	0.303		**No**

Abbreviations: CI = confidence interval; Diff = difference; PPG = postprandial glucose; H = hypothesis; HbA1c = hemoglobin A1c; LSM = least squares mean; MDI = multiple daily injections; NI = noninferiority comparison; NIM = noninferiority margin; SE = standard error; SP = superiority comparison.

Summary of Primary and Multiplicity Adjusted Efficacy Results for Phase 3 MDI Studies Using the Graphical Approach (Efficacy Estimand) (in % and mg/dL)

Hypothesis	Test	LSM (SE)		LY-Humalog LSM Diff (95% CI)	p-Value	NIM	Objective Met?
		Humalog	LY900014				
ITRM							
(H1) Change in HbA1c (%)	NI	-0.05 (0.031)	-0.13 (0.031)	-0.08 (-0.16, 0.00)		0.4%, 0.3%	**Yes**
		Humalog	**LY900014+20**				
(H5) Change in HbA1c (%)	NI	-0.05 (0.031)	0.08 (0.035)	0.13 (0.04, 0.22)		0.4%, 0.3%	**Yes**
		Humalog	**LY900014**				
(H2) 1 hr PPG excursion (mg/dL)	SP	74.3 (3.34)	46.4 (3.33)	-27.9 (-35.3, -20.6)	<0.001		**Yes**
(H3) 2 hr PPG excursion (mg/dL)	SP	103.9 (4.51)	72.7 (4.50)	-31.2 (-41.1, -21.2)	<0.001		**Yes**
(H4) Change in HbA1c (%)	SP	-0.05 (0.031)	-0.13 (0.031)	-0.08 (-0.16, 0.00)	0.060		**No**
ITRN							
(H1) Change in HbA1c (%)	NI	-0.43 (0.04)	-0.38 (0.04)	0.06 (-0.05, 0.16)		0.4%, 0.3%	**Yes**
(H2) Change 1 hr PPG excursion (mg/dL)	SP	74.9 (3.60)	63.1 (3.60)	-11.8 (-18.1, -5.5)	<0.001		**Yes**
(H3) Change 2 hr PPG excursion (mg/dL)	SP	97.8 (4.50)	80.4 (4.50)	-17.4 (-25.3, -9.5)	<0.001		**Yes**
(H4) Change in HbA1c (%)	SP	-0.43 (0.04)	-0.38 (0.04)	0.06 (-0.05, 0.16)	0.303		**No**

Abbreviations: CI = confidence interval; Diff = difference; H = hypothesis; HbA1c = hemoglobin A1c; LSM = least squares mean; MDI = multiple daily injections; NI = noninferiority comparison; NIM = noninferiority margin; PPG = postprandial glucose; SE = standard error; SP = superiority comparison.

In both Studies ITRM and ITRN, the primary objective was achieved; mealtime LY900014 was confirmed to be noninferior to Humalog for glycaemic control as measured by change in HbA1c at both NIMs of 0.4% and 0.3%.

Multiplicity-adjusted objectives (H2 and H3) were achieved; mealtime LY900014 was superior to Humalog in controlling 1-hour and 2-hour PPG excursions in the efficacy estimand.

Multiplicity-adjusted objective (H4) was not achieved; mealtime LY900014 was not superior to Humalog for glycaemic control as measured by change in HbA1c with the efficacy estimand. Similar results were observed in the ITT estimand. However, one difference between efficacy estimand and ITT analyses in the MDI studies was seen in ITRM. In T1D patients in ITRM, mealtime LY900014 was superior to Humalog for glycaemic control (H4) for the ITT estimand, though the efficacy estimand did not show superiority.

The sensitivity analyses for the efficacy and ITT estimands support the findings of the primary analyses in both T1D patients (ITRM) and T2D patients (ITRN).

The HbA1c results are given below for the ITT estimand:

ITRM (T1D):

From a similar baseline HbA1c level (7.33 %, 7.34 %, and 7.36 %), the change in HbA1c at week 26 was −0.00, −0.18 and +0.05 %-units for Humalog, LY900014, and LY900014+20, respectively (ITT estimand).

The LSM difference results for HbA1c (%) in the ITT estimand calculations for the different comparisons were as follows (95% CI), p-value, at week 26:

- LY900014 vs. Humalog: -0.08 (-0.161,-0.003), p=0.041
- LY900014+20 vs. Humalog: 0.14 (0.053, 0.226), p=0.002
- LY900014+20 versus LY900014: 0.22 (0.136,0.307), p<0.001

ITRN (T2D):

From a similar baseline HbA1c level (Humalog 7.31 %, LY900014 7.28 %), the change in HbA1c at week 26 was −0.46 and −0.43 %-units for Humalog and LY900014 respectively (ITT estimand).

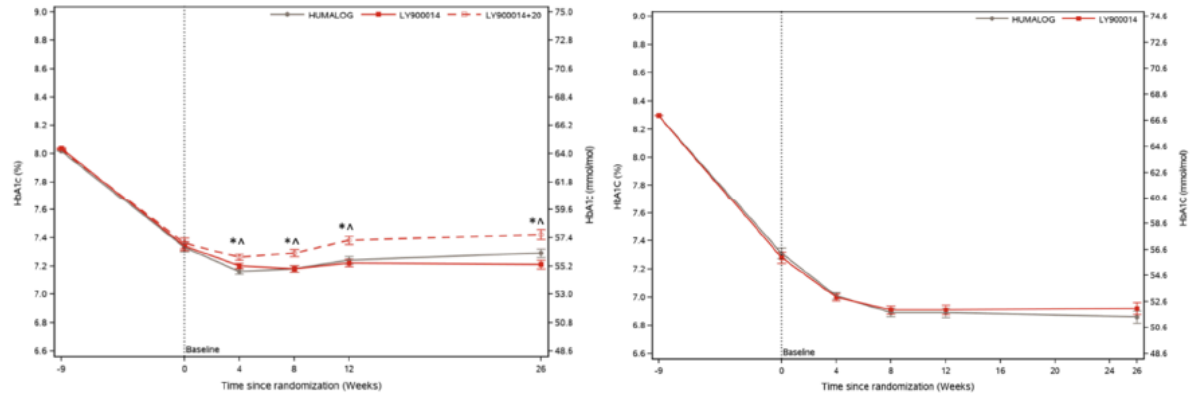
The LSM difference for HbA1c (%) in the ITT estimand calculation was as follows (95% CI), p-value, at week 26:

- LY900014 vs. Humalog: 0.03 (−0.08,0.13), p=0.624

Evolution of glycaemic control during the study

As the studies were conducted according to the treat-to-target principle, there was a marked improvement in glycaemic control in all study arms in T1D (ITRM) and T2D (ITRN). Most of the improvement already occurred during the lead-in period, when basal insulin was titrated to be optimal, and all patients were administered Humalog as prandial insulin. Some further improvement occurred during the intensive titration phase, when prandial insulins were titrated to optimal (figure 41).

Figure 41. Change in HbA1c, studies ITRM (T1D) and ITNR (T2D)



ITRM ITRN

*p<0.05 for pairwise comparison LY900014+20 versus Humalog
^p<0.05 for pairwise comparison LY900014+20 versus LY900014
Note 2: Data are Mean at study entry and LSM ± SEM at other visits.
Note 1: The conversion between % and mmol/mol is 10.93*Hba1c(%) - 23.5
Abbreviations: HbA1c = hemoglobin A1c; LSM = least squares mean;
SEM = standard error of the mean.

The actual HbA1c levels and change from baseline are given in Table 18.

Table 18. HbA1c actual and change in studies ITRM (T1D) and ITRN (T2D) Efficacy estimand

Treatment Group	HbA1c, LSM (SE)			LSM Diff at Week 26
	Baseline	Week 26	Change from Baseline at Week 26	A: LY900014 - Humalog (95% CI), p-value B: LY900014+20 - Humalog (95% CI), p-value C: LY900014+20 - LY900014 (95% CI), p-value
ITRM, HbA1c (mmol/mol)				
Humalog	56.7 (0.34)	56.1 (0.34)	-0.6 (0.34)	A: -0.8 (-1.7, 0.0), p=0.060
LY900014	56.7 (0.34)	55.3 (0.33)	-1.4 (0.33)	B: 1.4 (0.5, 2.4), p=0.003
LY900014+20	56.9 (0.40)	57.6 (0.39)	0.8 (0.39)	C: 2.3 (1.3, 3.2), p<0.001
ITRN, HbA1c (mmol/mol)				
Humalog	56.4 (0.42)	51.5 (0.46)	-4.7 (0.46)	A: 0.6 (-0.6, 1.8), p=0.303
LY900014	56.0 (0.42)	52.1 (0.46)	-4.1 (0.46)	
ITRM, HbA1c (%)				
Humalog	7.33 (0.03)	7.29 (0.03)	-0.05 (0.03)	A: -0.08 (-0.16, 0.00), p=0.060
LY900014	7.34 (0.03)	7.21 (0.03)	-0.13 (0.03)	B: 0.13 (0.04, 0.22), p=0.003
LY900014+20	7.36 (0.04)	7.42 (0.04)	0.08 (0.04)	C: 0.21 (0.12, 0.29), p<0.001
ITRN, HbA1c (%)				
Humalog	7.31 (0.04)	6.86 (0.04)	-0.43 (0.04)	A: 0.06 (-0.05, 0.16), p=0.303
LY900014	7.28 (0.04)	6.92 (0.04)	-0.38 (0.04)	

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

Mixed Meal Tolerance Test

In both MDI studies, LY900014 was superior to Humalog in controlling 1- and 2-hour PPG excursions following the MMTT, when both were administered 0-2 minutes prior to meal. The results for ITRM are given in table 19 and figure 42 (efficacy estimand).

Table 19. PPG excursions following test meal; ITRM (T1D) and ITRN (T2D)

Treatment Group	Serum Glucose, LSM (SE)			LSM Diff at Week 26 A: LY900014 - Humalog (95% CI), p-value B: LY900014+20 - Humalog (95% CI), p-value C: LY900014+20 - LY900014 (95% CI), p-value
	Baseline	Week 26	Change from Baseline at Week 26	
1 hr Post Meal Serum Glucose (mmol/L)				
ITRM				
Humalog	3.97 (0.168)	4.13 (0.185)	-0.04 (0.185)	A: -1.55 (-1.96, -1.14), <0.001 B: 0.73 (0.28, 1.19), 0.002 C: 2.28 (1.83, 2.73), <0.001
LY900014	4.29 (0.166)	2.57 (0.185)	-1.59 (0.185)	
LY900014+20	4.24 (0.199)	4.86 (0.207)	0.70 (0.207)	
ITRN				
Humalog	4.28 (0.141)	4.16 (0.200)	-0.11 (0.200)	A: 0.66 (-1.01, -0.30), <0.001
LY900014	4.25 (0.142)	3.50 (0.200)	-0.77 (0.200)	
2 hr Post Meal Serum Glucose (mmol/L)				
ITRM				
Humalog	5.64 (0.244)	5.77 (0.250)	-0.20 (0.250)	A: -1.73 (-2.28, -1.18), <0.001 B: -0.37 (-0.98, 0.24), 0.235 C: 1.36 (0.75, 1.97), <0.001
LY900014	6.26 (0.241)	4.04 (0.250)	-1.93 (0.250)	
LY900014+20	5.99 (0.290)	5.40 (0.280)	-0.56 (0.280)	
ITRN				
Humalog	5.53 (0.192)	5.43 (0.250)	-0.09 (0.250)	A: -0.96 (-1.41, -0.52), <0.001
LY900014	5.51 (0.192)	4.47 (0.250)	-1.06 (0.250)	

The results on the ITT analysis are concordant with the efficacy estimand analysis.

The first (H2) and second (H3) multiplicity adjusted objectives were achieved.

LY900014 was statistically superior to Humalog in controlling 1-hour and 2-hour PPG excursions in both T1D and T2D.

In T1D (ITRM),

- At 1 hour, the LSM difference was −1.53 mmol/L (p<0.001; ITT estimand)
- At 2 hours, the LSM difference was −1.69 mmol/L (p<0.001; ITT estimand)

In T2D (ITRN),

- At 1 hour, the LSM difference was −0.67 mmol/L (p<0.001; ITT estimand)
- At 2 hours, the LSM difference was −0.98 mmol/L (p<0.001; ITT estimand)

The PPG excursions were significantly lower in the LY900014 group vs. Humalog group from the time point of 15 minutes after the test meal up to 4 hours post-meal in T1D and from 30 minutes after the test meal up to 4 hours post-meal in T2D (Figure 3.3.5.5).

Mean PPG excursions in T1D patients (ITRM) according to the ITT estimand at Week 26 were as follows in the different study arms:

LY900014 versus Humalog:

- statistically significantly lower at all time points from 15 minutes to 4 hours

LY900014+20 versus Humalog:

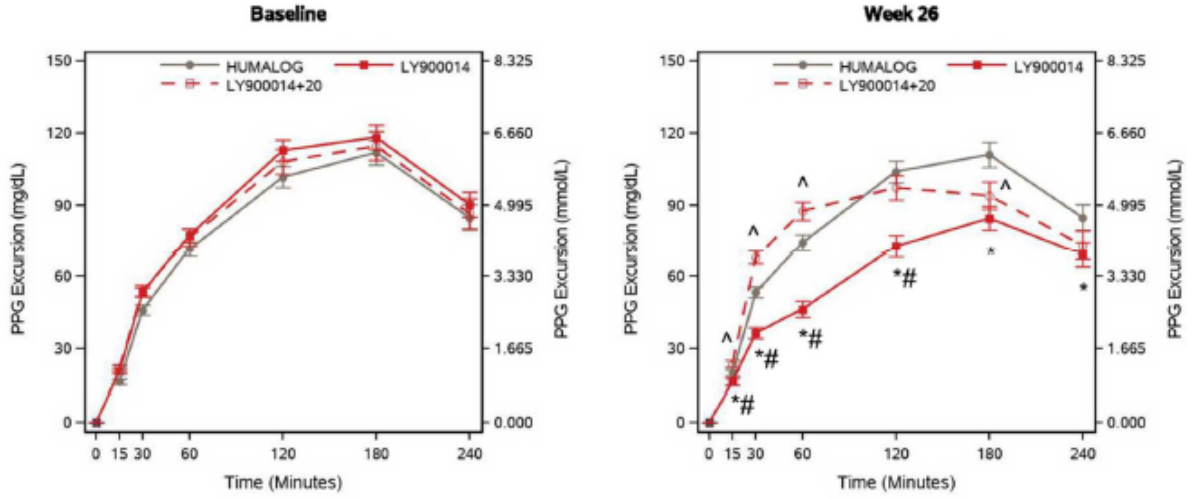
- statistically significantly higher at 30 minutes, 1 hour
- similar in both groups at 15 minutes, 2 hours and 4 hours
- statistically significantly lower at 3 hours

LY900014+20 versus LY900014:

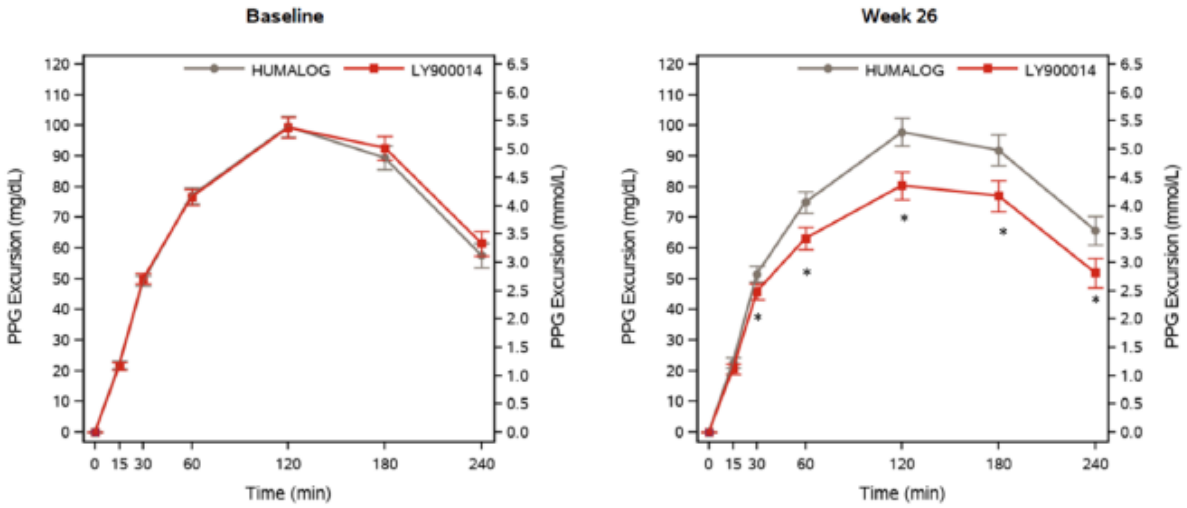
- statistically significantly higher at 15 minutes, 30 minutes, 1 hour, and 2 hours

- similar in both groups at 3 hours and 4 hours

Figure 42. Study ITRM (T1D, top) and ITRN (T2D, bottom) PPG excursions during MMTT performed at baseline, prior to randomization (all patients received Humalog), and after 26 weeks of treatment (efficacy estimand)



*p<0.05 for pairwise comparison on LY900014 versus Humalog
^p<0.05 for pairwise comparison on LY900014+20 versus Humalog
#p<0.05 for pairwise comparison on LY900014+20 versus LY900014



*p<0.05 for LY900014 versus Humalog

Abbreviation: min = minutes; PPG =postprandial glucose; SE = standard error.

<u>iAUC and glucose variability during MMTT (ITRM, T1D)</u>

Incremental areas under the serum glucose concentration-time curve (iAUC) were determined in the ITRM (T1D) based on samples collected in the MMTT from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after a meal. Maximum serum glucose after a meal was collected, and glucose variability measured by the coefficient of variation and standard deviation (SD). The results for the time

periods 0−30 min, 0−60 min, 0−120 min, 0−180 min, and 0−240 min are separately tabulated in the interim CSR for baseline and 26 weeks (in units [mg*min/dL], data not included in this AR).

At Week 26, the iAUC during MMTT was:

- statistically significantly lower in LY900014 versus Humalog at all time intervals (0-30 minutes, 0-1 hour, 0-2 hours, 0-3 hours, and 0-4 hours)
- statistically significantly higher in LY900014+20 versus Humalog at 0-30 minutes and 0-1 hour, but similar at 0-2 hours, 0-3 hours, and 0-4 hours
- statistically significantly higher in LY900014+20 versus LY900014 at all time intervals (0-30 minutes, 0-1 hour, 0-2 hours, 0-3 hours, and 0-4 hours).

The iAUC results from ITRM are concordant with the primary and multiplicity-adjusted secondary endpoints.

In ITRM, glucose variability was derived from the glucose values collected during MMTT. A small difference was seen in the standard deviation (SD) of blood glucose during in favour of LY900014 vs. Humalog: the difference in SD was 0.43 mmol/L (2.97 versus 3.40 mmol/L, $p<0.001$). There was no difference between LY900014+20 vs. Humalog. However, SD was higher when LY900014 was given postprandially vs. preprandially: difference in SD 0.23 mmol/L (3.21 versus 2.97 mmol/L, $p=0.027$). The other measure of variability, coefficient for variation (CV) demonstrated no differences between the products over the time of MMTT. These minor differences are not considered clinically relevant.

Continuous Glucose Monitoring (CGM) substudy in ITRM (T1D)

A total of 269 patients who received at least 1 dose of study treatment and wore the CGM device during at least 1 collection period (either baseline or postbaseline) (LY900014, 97; Humalog, 99; LY900014+20, 73) were included in the CGM analyses.

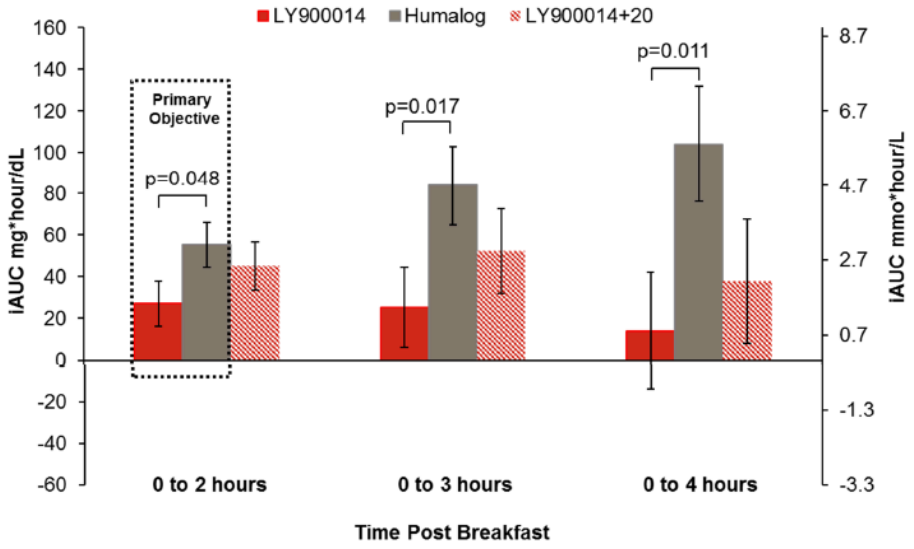
Incremental Glucose AUC

LY900014 statistically significantly reduced the postprandial glucose $iAUC_{0\text{-}2hrs}$ after breakfast at Week 26 when compared to Humalog (approximately 51% reduction). These reductions were also statistically significant for comparisons of iAUC0-3hrs (approximately 70% reduction) and $iAUC_{0\text{-}4hrs}$ (approximately 87% reduction) (Figure 43).

The iAUC for mealtime LY900014 was also statistically significantly lower than Humalog for all time intervals tested when all meals were combined.

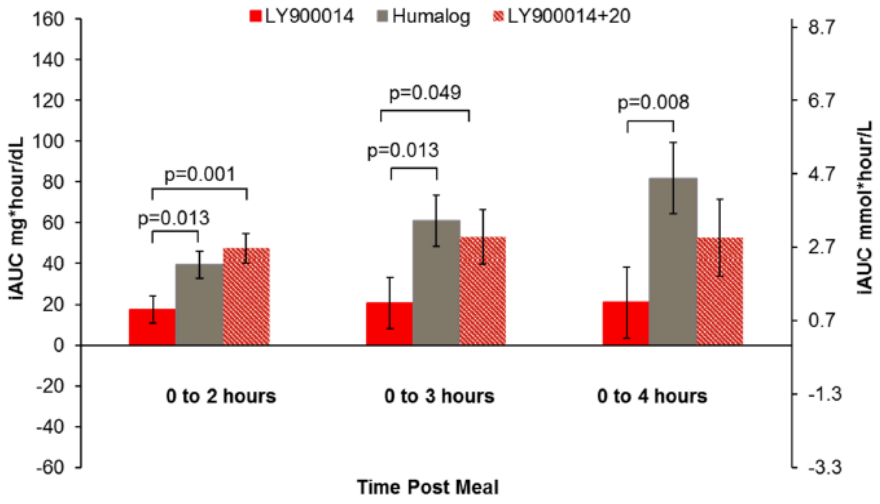
LY900014+20 was not statistically significantly different in postprandial glucose iAUC for any time interval for breakfast or for all meals combined versus Humalog. LY900014+20 was statistically significantly higher than LY900014 in postprandial glucose iAUC at 2 and 3 hours for all meals combined (Figure 44).

Figure 43. iAUC after breakfast at Week 26, I8B-MC-ITRM CGM substudy (T1D)



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

Figure 44. iAUC after all meals at Week 26, I8B-MC-ITRM CGM substudy (T1D)

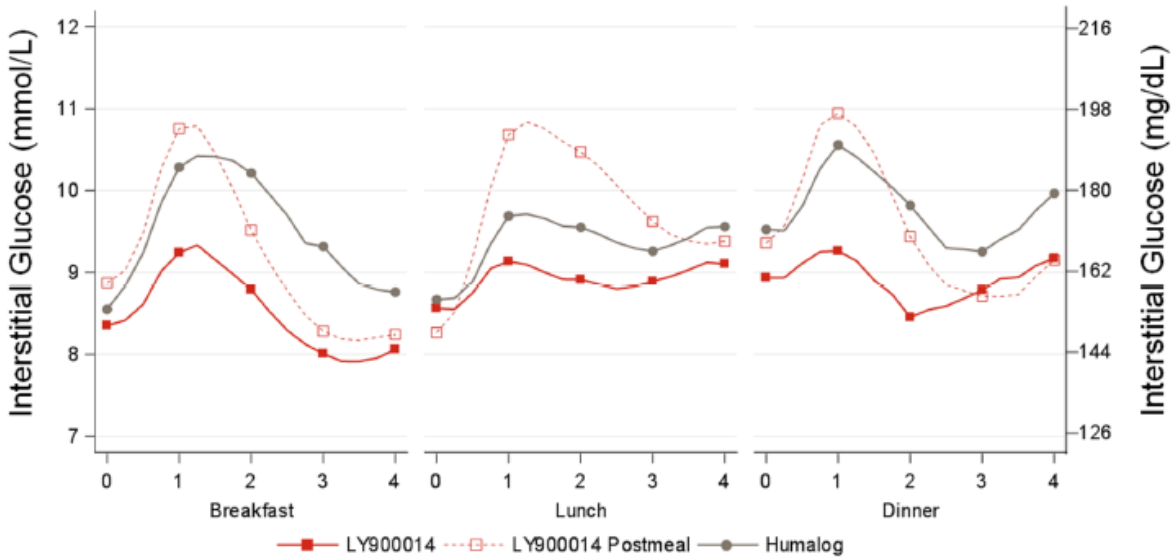


Abbreviations: iAUC = incremental area under the curve; LSM = least squares mean; SE = standard error.
Data are LSM (SE)
Source: /lillyce/prd/ly900014/i8b_mc_itrm/csr1/output/shared/smcga01.rtf.

Ambulatory Glucose

The mean ambulatory glucose profiles for the 4-hour period following breakfast, lunch, and dinner at Week 26 from which the glucose iAUC results presented above were derived. At baseline, all patients were given Humalog and the PPG profiles were similar for all treatment groups. At Week 26, PPG control was better in the LY900014 group compared to the Humalog group. At Week 26, LY900014+20 was less effective in managing PPG compared to mealtime LY900014 at all meals throughout the day and was less effective compared to Humalog primarily during lunch.(Figure 45).

Figure 45. Ambulatory PPG profiles from CGM monitoring performed prior to the 26-week endpoint. ITRM CGM substudy. T1D

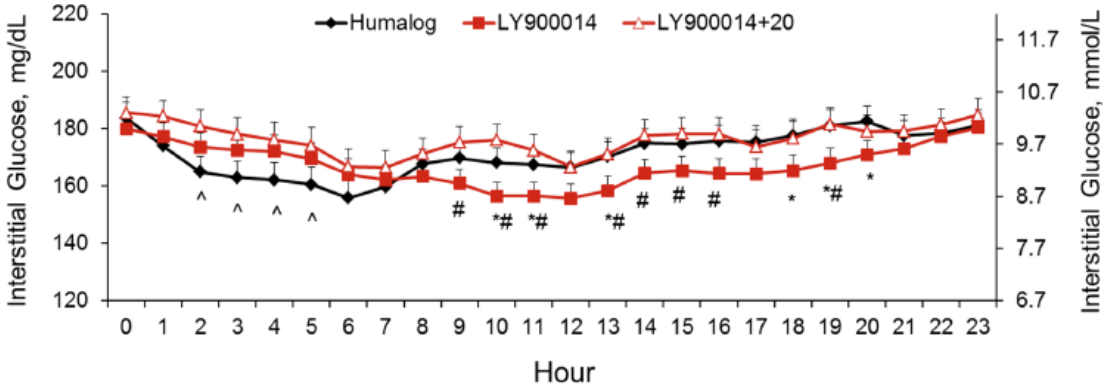


Abbreviation: CGM = continuous glucose monitoring.

Time in Glucose Target Range

The 24-hour glucose profile in each treatment group from CGM was examined. This analysis was discussed and approved by CHMP during scientific advice (2016). Statistically significantly lower glucose levels were observed for LY900014 compared to Humalog during the daytime hours. Average glucose between 02:00 and 05:00 AM was statistically significantly higher in LY900014+20 compared to Humalog. Significance and hourly averages are illustrated in Figure 46.

Figure 46. Hourly average glucose by CGM at Week 26. CGM substudy. T1D



Abbreviations: LSM = least squares mean; SE = standard error.
*p<0.05, LY900014 versus Humalog
^p<0.05, LY900014+20 versus Humalog
#p<0.05, LY900014+20 versus LY900014
Values are LSM+SE

Proportion of patient achieving HbA1c targets – ITRM (T1D), ITRN (T2D)

The analyses on subjects achieving HbA1c target ≤6.5% and <7% in studies ITRM and ITRN are tabulated in Table 20.

In ITRM (T1D), no statistically significant treatment differences were seen between the LY900014 and Humalog groups in the percentages of patients achieving HbA1c targets (≤6.5% and <7%) at Week 26. However, postprandial administration of LY90014 (group LY900014+20) was less effective than Humalog and preprandial LY90014 in terms of achieving these target levels.

In ITRN (T2D), no statistically significant differences were seen in the proportions of patients achieving HbA1c targets at any time point.

Table 20. T1D(ITRM) and T2D(ITRN) patients achieving HbA1c targets ≤6.5% and <7%

Treatment Group	Proportion Achieving HbA1c Targets (n [%])		Odds Ratio at Week 26 A: LY900014 / Humalog (95% CI), p-value B: LY900014+20 / Humalog (95% CI), p-value C: LY900014+20 /LY900014 (95% CI), p-value
	Baseline	Week 26	
ITRM, HbA1c ≤6.5%			
Humalog	46 (10.4)	65 (15.6)	A: 1.16 (0.75, 1.78), 0.508 B: 0.60 (0.36, 0.99), 0.046 C: 0.52 (0.32, 0.85), 0.009
LY900014	48 (10.7)	72 (16.8)	
LY900014+20	23 (7.1)	31 (10.0)	
ITRN, HbA1c ≤6.5%			
Humalog	42 (12.5)	113 (35.3)	A: 1.02 (0.72, 1.45), 0.912
LY900014	44 (13.2)	121 (38.3)	
ITRM, HbA1c <7%			
Humalog	137 (31.0)	140 (33.6)	A: 1.23 (0.88, 1.73), 0.222 B: 0.63 (0.44, 0.91), 0.014 C: 0.51 (0.35, 0.74), <0.001
LY900014	133 (29.6)	160 (37.4)	
LY900014+20	79 (24.5)	79 (25.6)	
ITRN, HbA1c <7%			
Humalog	103 (30.8)	168 (52.5)	A: 1.24 (0.87, 1.77), 0.238
LY900014	113 (33.8)	184 (58.2)	

Abbreviations: CI = confidence interval; HbA1c = hemoglobin A1c; n = number of patients in the specified category.

10 point SMBG at Week 26 – ITRM (T1D), ITRN (T2D)

ITRM (T1D)

Daily mean BG excursions from pre-meal to 1- and 2-hours post-meal were significantly lower in the LY900014 group than in the Humalog group. Significant differences in favour of LY900014 were seen also after lunch and after dinner. However, the mean and pre-meal daily mean glucose levels did not differ between LY900014 and Humalog.

Postprandial administration of LY900014 (LY900014+20) produced similar daily mean and pre-meal daily mean glucose levels in comparison with Humalog. However, SMBG values were significantly higher at 1 hour following lunch and dinner in the LY900014+20 arm vs. Humalog arm, but not statistically significantly in any other time point. The higher post-lunch and post-dinner values were also reflected in a significantly higher mean 1-hour post-meal glucose and daily mean excursion from evening pre-meal to 1-hour post-meal and daily mean pre-meal to 1-hour post-meal (Figure 47).

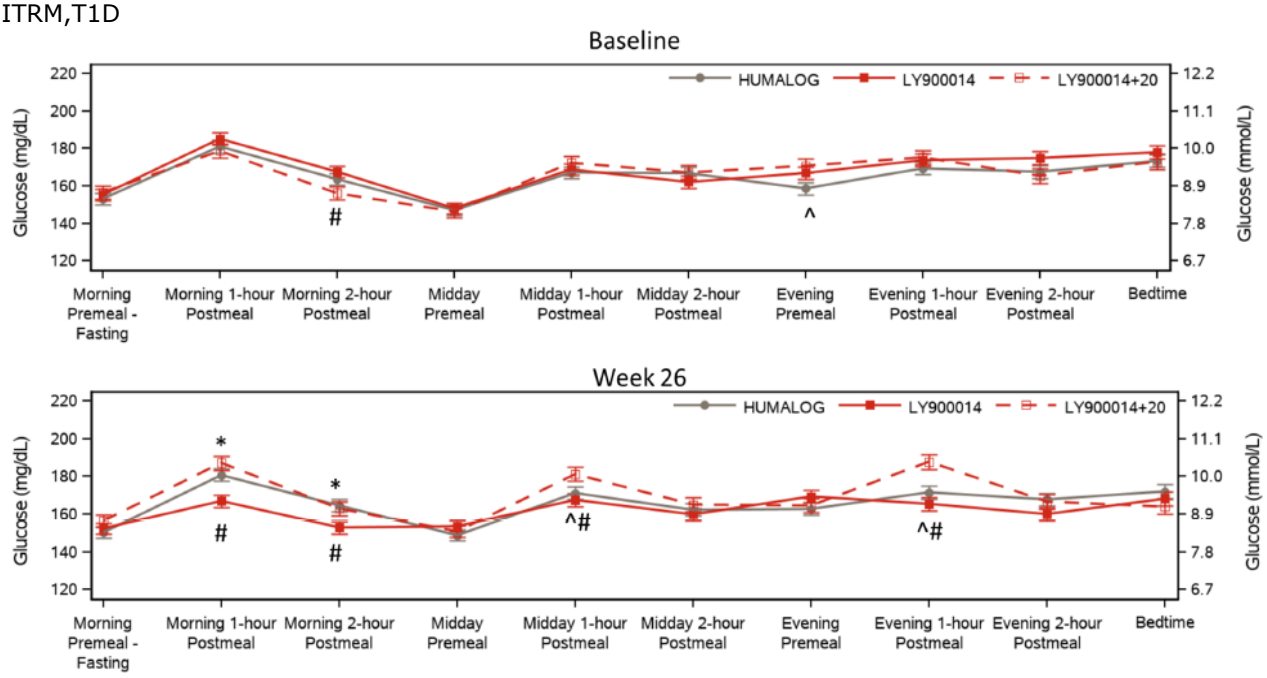
In comparison with LY900014, LY900014+20 produced similar pre-meal daily mean glucose levels; however, the overall daily mean glucose was statistically significantly higher, in favour or preprandial

administration of LY900014. This was caused by significantly higher daily mean BG excursions from pre-meal to 1- and 2-hour postmeal levels compared to LY900014 (Figure 48).

ITRN (T2D)

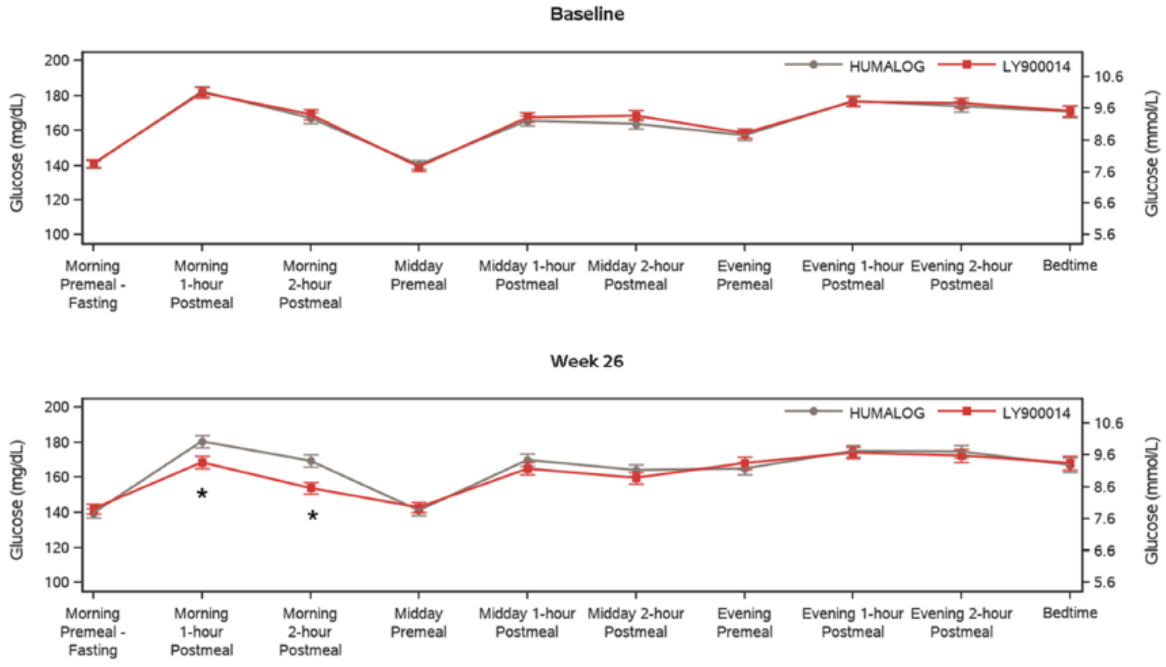
LY900014 exhibited statistically significantly lower daily mean blood glucose excursions from pre-meal to 1- and 2-hour post-meal compared to Humalog. LY900014 also statistically significantly decreased SMBG at 1 and 2-hour post morning meal compared to Humalog with no statistically significant treatment differences at any other 10-point SMBG time point. Overall, the glucose fluctuations between LY900014 and Humalog are more similar in T2D subjects than in T1D subjects (Figure 49).

Figure 47. Time course of 10-point SMBG profile at baseline and Week 26, all randomized patients. ITRM,T1D



Abbreviations: LSM = least squares mean; SEM =standard error of the mean.
*p<0.05 for pairwise comparison LY900014 versus Humalog
^p<0.05 for pairwise comparison LY900014+20 versus Humalog
#p<0.05 for pairwise comparison LY900014+20 versus LY900014
Data are LSM ± SEM

Figure 48. Time course of 10-point SMBG profile at baseline and Week 26, all randomized patients. ITRN,T2D



Data are LSM (SE)
*p<0.001

Abbreviations: LSM = least squares mean; SE = standard error.

Upon request, the Applicant conducted simulations on what would happen if the patient injected LY900014 or Humalog and would not eat thereafter, using the PK/PD model parameters. Simulations were conducted by controlling variables affecting glycaemic response (dose of insulin, glucose level, etc.) Simulations for patients with T1D and T2D were conducted using the corresponding population PK/PD model. Based on PK/PD modelling, the Applicant demonstrated that onset of hypoglycaemia is slightly faster for Liumjev compared to Humalog in the T1D but not the T2D population. The proportion of patients that is predicted to reach the hypoglycaemia threshold, both in the T1D and the T2D population, is similar in Humalog and Liumjev treated groups.

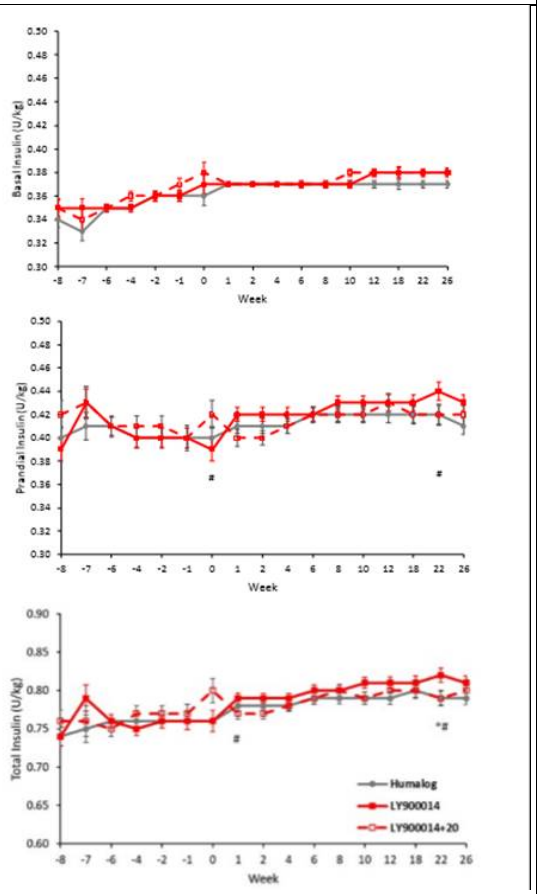
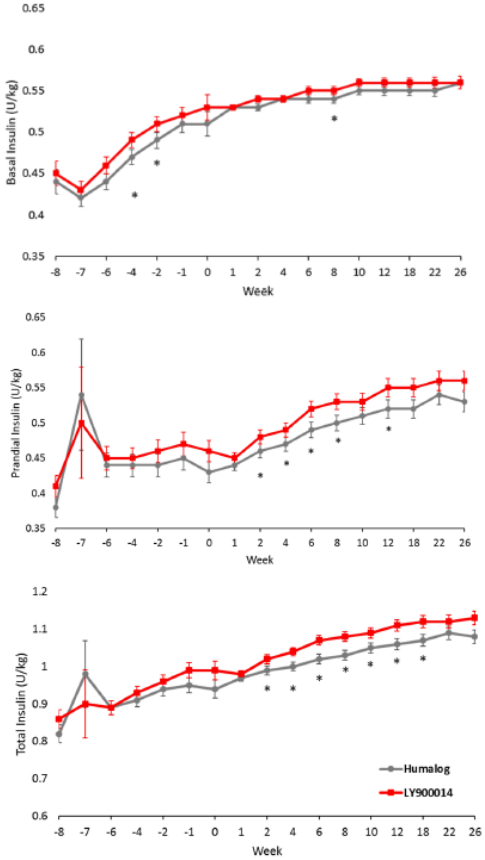
Insulin dose

In ITRM (T1D), at week 26, there were no statistically significant differences between treatments in basal, prandial, and total daily insulin doses. The prandial to total insulin ratio at week 26 ranged from 51.3% to 52.1% in the different study arms.

In ITRN (T2D), at Week 26, the basal insulin dose was not statistically significantly different between treatments. The LY900014 prandial and total insulin doses were higher at Week 26 than Humalog; however once adjusted for weight no statistically significant differences were present. The prandial to total insulin ratio at Week 26 was also similar: Humalog: 48.5%, LY900014: 49.7%.

In all study arms, insulin doses increased during the study, more markedly in T2D patients (Figure 49).

Figure 49. Basal, prandial, and total daily insulin doses (U/kg) during the 8-week lead-in period and 26 week treatment period, all randomised patients

ITRM (T1D)	ITRN (T2D)
	

Serum 1,5 anhydroglucitol

ITRM (T1D)

1,5-AG levels increased (improved) from baseline to week 26 in in patients treated for 26 weeks with mealtime LY900014 and decreased in Humalog and LY900014+20 groups (LSM change: LY900014, 0.19 mg/dL; Humalog, -0.22 mg/dL; LY900014+20, -0.38 mg/dL). At Week 26, 1,5-AG levels (LSM) were statistically significantly higher in LY900014 (5.04 mg/dL) versus Humalog (4.64 mg/dL, p=0.003) and versus LY900014+20 (4.48 mg/dL, p<0.001).

ITRN (T2D)

1,5 AG levels increased (improved) to a similar extent during treatment with Humalog and LY900014 (LSM change at Week 26: Humalog, 2.15 mg/dL; LY900014, 1.99 mg/dL; p=0.600). As the test 1,5-AG is not yet a standard test, the clinical relevance of the change that was seen in study ITRM is not clear. Furthermore, there was no difference in 1,5 AG levels in ITRN (T2D), although a difference was seen in postprandial control. The Applicant discussed that there were more confounding factors in T2D patients, including concomitant oral antihyperglycaemic agents, especially SGLT2 inhibitors, which cause glucosuria and may according to literature decrease 1,5 AG levels. Furthermore, the difference in postprandial glycaemic control between Humalog and LY900014 was smaller in T2D than in T1D. Overall, the clinical relevance of the 1,5-AG results in the well-controlled study participants of ITRM and ITRN is not clear; and this measure is not widely used in clinical practice.

Efficacy results of ITSI

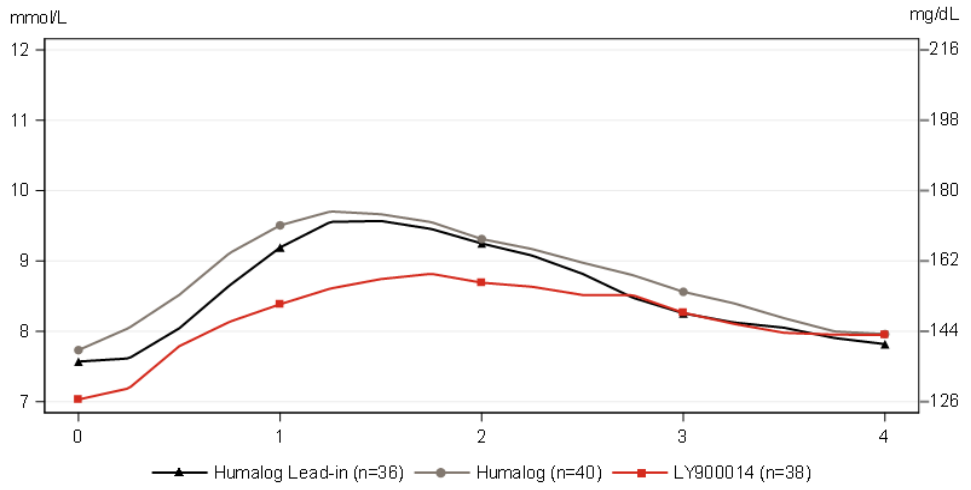
The study was not powered to show statistical differences between study arms; hence, the results are descriptive.

There was no difference between study arms in insulin dose (basal, bolus, total daily dose).

All patients entered Study ITSI under good glycaemic control, which was further improved in the first 6 weeks (Period I) and maintained throughout Period II. In Period I, both treatments showed statistically significant reductions from baseline. The LY900014-treated patients had a numerically greater reduction in mean HbA1c, even though the baseline was lower (data not shown for brevity).

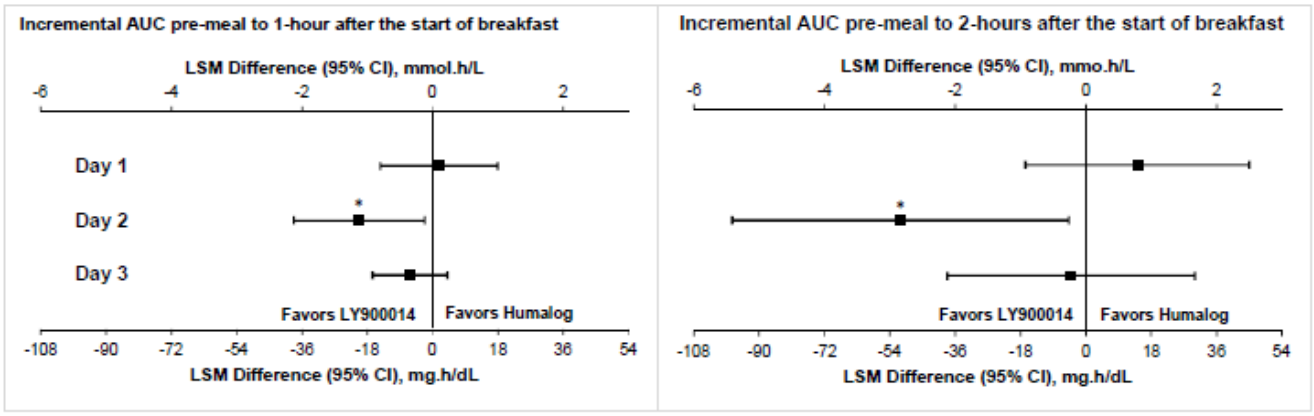
In ITSI, a trend for better glycaemic control post-breakfast and other indices of improved glycaemic control were consistently observed for LY900014 compared to Humalog as shown in the ambulatory glucose profile, postmeal iAUCs and time with glucose in target ranges (Figures 3.3.5.13−3.3.5.15). The study was not powered to show statistically significant difference in efficacy measures.

Figure 50. Study ITSI (T1D) plot of ambulatory glucose profiles (mean profiles) for 0 to 4 hours post-breakfast for the CGM population during Weeks 4 to 6 of the 6-week treatment period



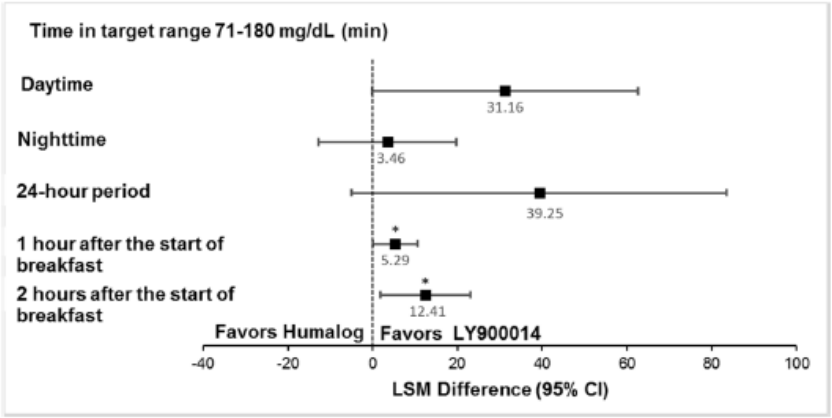
Notes: 0 hr mean is calculated as the average of the CGM values in the time window [-19, 0] mins relative to the start of the meal.
Notes: Mean lines are calculated at 15 minute intervals relative to meal start time using locally weighted polynomial regression (0.15 smoothing).
Notes: Only subjects with non-missing baseline and post-baseline values of the response variable were included in analysis.

Figure 51. Postmeal (breakfast) incremental AUCs for Weeks 4 to 6 of the 6-week treatment period by infusion set wear day. ITSI (T1D)



Abbreviations: AUC = area under the curve; CI = confidence interval; LSM = least squares mean.
* $p<0.05$.

Figure 52. Time with glucose in target ranges for Weeks 4 to 6 of the 6-week treatment period. ITSI (T1D)



Abbreviations: AUC = area under the concentration versus time curve; CI = confidence interval; LSM = Least Squares mean.

Interstitial glucose reduction rate from hyperglycaemia to recovery (≤10mmol/l) was assessed for the following threshold of hyperglycaemia throughout each 6 week period: >10.0 mmol/L, > 10.0 mmol/L and ≤13.9 mmol/L,>13.9 mmol/L and ≤16.7 mmol/L, and >16.7 mmol/L. The LSM rate of interstitial glucose reduction to recovery was statistically significantly faster for LY900014 treatment (0.03 mmol/L/min) compared to Humalog treatment (0.01 mmol/L/min) for Weeks 0 to 6. For the other thresholds no significant differences were observed.

Health outcomes analyses

The Insulin Treatment and Satisfaction Questionnaire (ITSQ) was collected as secondary endpoint in the MDI studies. ITSQ includes the domains inconvenience, lifestyle, hypoglycaemic control, glycaemic control, and delivery system, and an overall transformed score. In ITRN, there was a difference in one of the individual domains, the insulin delivery device treatment satisfaction transformed score, that was higher in the Humalog group (88.4) than in the LY900014 group (77.6) (LSM change: 1.0 versus -1.5; p=0.021) at LOCF endpoint. No statistically significant treatment differences were seen in any other ITSQ

domain transformed score or overall transformed score at baseline or Week 26. This is regarded as a chance finding, since similar blinded prefilled pens were used in both study arms.

The EQ-5D-5, VAS score, and the Work Productivity and Activity Impairment Questionnaire (WPAI) were tertiary/exploratory endpoints in ITRM (T1D) and ITRN (T2D). No statistically significant treatment differences were observed either in the EQ-5D-5L health state index scores or the VAS score.

The WPAI includes the following domains: overall work impairment, absenteeism, presenteeism, and outside of work activity impairment. The only difference in one of the domains was noted at baseline (outside of work activity impairment), however, during the treatment phase and at the end no differences evolved between study arms.

It is obvious that none of the health outcome (HO) measures was designed to capture patients' wellbeing in the postprandial state or symptoms of hyperglycaemia, such as postprandial alertness/sleepiness or mood changes. Hence, it is not surprising that no relevant differences were observed in these HO measures.

Ancillary analyses

Sensitivity analyses were conducted on the primary endpoint (change in HbA1c from baseline to Week 26) and secondary endpoint (1h and 2h glucose excursions during MMTT) in ITRM and ITRN. Missing-at-random (MAR) analyses were conducted. Primary analysis model was also repeated using the per protocol and completer populations. The sensitivity analyses supported non-inferiority of LY900014 vs. Humalog on overall glycaemic control as measured by HbA1c level and superiority of LY900014 to Humalog in controlling 1-hour and 2-hour PPG excursions during mixed meal tolerance test (data not included in this AR).

Subgroup analyses were performed in ITRM and ITRN from baseline to endpoint. The change in HbA1c from baseline to the primary endpoint (Week 26) for various subgroups was analysed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit, and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 26) was evaluated to assess the treatment by subgroup interaction.

The analysed subgroups are listed in Table 21.

One statistically significant (p=0.084) treatment-by-subgroup interaction was observed in the subgroup analyses of ITRM (T1D): Subgroup of baseline 2-hour PPG at baseline ≤10/mmol/L and 10/mmol/L. The 95% CIs for both PPG subgroups led to the same conclusion in noninferiority.

In the subgroup analyses of ITRN (T2D), there was a statistically significant difference in treatment by subgroup interaction at Week 26 based on MMRM for the subgroup of baseline HbA1c (≤8.0% and 8.0%). The magnitude of treatment difference at Week 26 was smaller in the baseline HbA1c ≤8.0% category than in the baseline HbA1c >8.0% category although the 95% CIs for both categories included zero. There was also a significant difference in the treatment by subgroup interaction for the subgroup of body mass index (BMI<35 kg/m2 vs.≥35 kg/m2). The treatment difference showed an increase in HbA1c in the baseline BMI <35 kg/m2 category, but showed a decrease in the baseline BMI ≥35 kg/m2 category. Although the directions of LSM difference were different, the 95% CI for both BMI categories led to the same conclusion in noninferiority.

As a conclusion on subgroup analyses, consistent treatment effects across subgroup analyses were observed in comparison of LY900014 with Humalog based on patient characteristics, diabetes characteristics and geographic areas, with the three exceptions described by the Applicant. Statistically

significant differences in glycaemic response were seen in T1D subjects (in the subgroup divided by baseline 2-hour PPG at baseline ≤10 mmol/L vs. >10 mmol/L) and in T2D subjects (in the subgroup of baseline HbA1c at ≤ 8.0% and >8.0% and the subgroup of BMI at <35 kg/m2 and ≥35 kg/m2); at the significance level of 0.1. The noted treatment-by-subgroup interactions are not considered clinically relevant.

Table 21. Subgroup Analyses of HbA1c in Studies ITRM (T1D) and ITRN (T2D)

	Study ITRM	Study ITRN
Age	<40, ≥40 years	<65, ≥65 years
Baseline 1-hour PPG (≤180, >180 mg/dL)	Yes	Yes
Baseline 1-hour PPG Excursion	Yes	Yes
Baseline 2-hour PPG (≤180, >180 mg/dL)	Yes	Yes
Baseline 2-hour PPG Excursion	Yes	Yes
Baseline HbA1c Stratum	≤7.5%, >7%	≤8%, >8%
Body Mass Index	<25 vs ≥25 kg/m^2	<25 vs ≥25 kg/m^2
	<30 vs ≥30 kg/m^2	<30 vs ≥30 kg/m^2
	No	<35 vs ≥35 kg/m^2
Country	Yes	Yes
Duration of Diabetes	Yes	Yes
Ethnicity	Yes	Yes
Personal CGM/FGM Use During the Study (Yes, No)	Yes	No
Prandial Insulin Dosing Plan	Yes	No
Number of Prandial Doses at Study Entry (<3, ≥3)	No	Yes
Race	Yes	Yes
Region	Yes	Yes
Sex (Male, Female)	Yes	Yes
Type of Basal Insulin During the Lead-in Period	Yes	Yes
SGLT-2 inhibitor treatment	No	Yes

Abbreviations: CGM = continuous glucose monitoring; FGM = flash glucose monitoring; HbA1c = hemoglobin A1c; No = subgroup analysis not conducted; PPG = postprandial glucose; SGLT-2 = sodium-glucose cotransporter-2; Yes = subgroup analysis conducted.

Long-term maintenance results for efficacy (ITRM, 52 weeks)

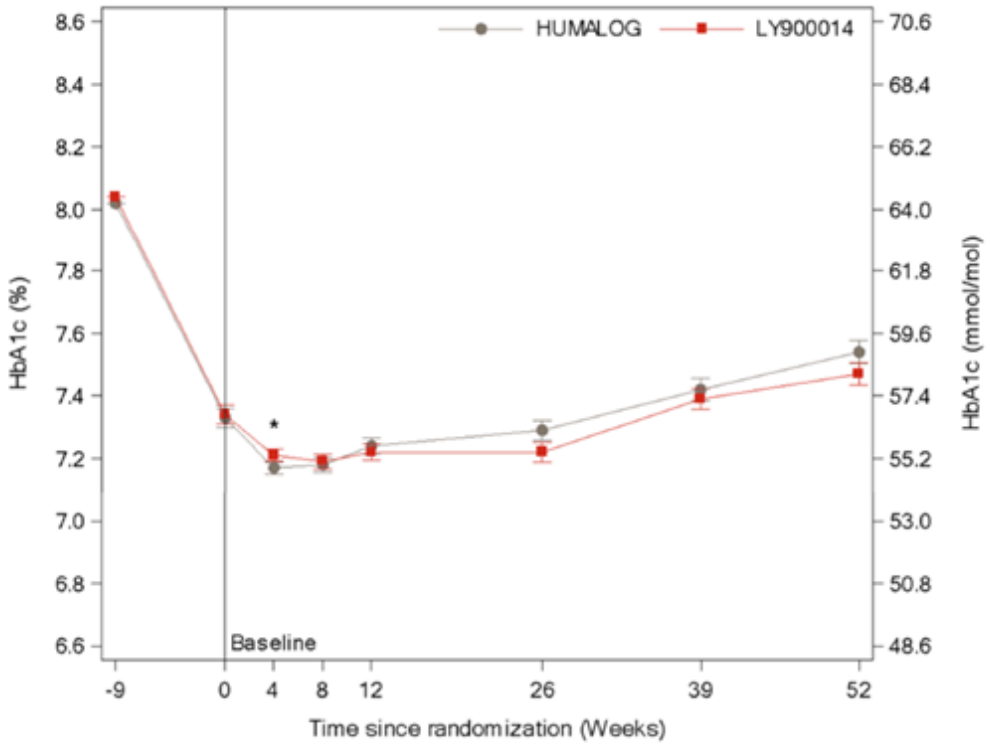
With their D121 response, the Applicant submitted the final ITRM CSR with results of the long-term maintenance period (26-52 weeks) and safety follow-up period (4 week period after week 52) comparing in a double-blind manner the safety and efficacy of prandial LY900014 vs. prandial Humalog, and safety results for the LY900014+20 group for the 4-week safety follow-up (weeks 26-30) and the remaining safety results for ITRN.

Approximately 92% of patients completed the ITRM study and the treatment. All randomized patients in the double-blind treatment groups (LY900014, n=451; Humalog, n=442) were included in the efficacy analyses. The demographic and other baseline characteristics were balanced between the groups.

In both double-blind treatment groups, HbA1c similarly improved during the lead-in and intensive titration period (Weeks 0 to 12), remained stable during the maintenance period (Week 12 to 26), increased marginally during the long-term maintenance period (Weeks 26 to 52), and was not statistically significantly different between treatments at the 52-week endpoint.

The proportions of patients meeting HbA1c targets were similar in the double-blind treatment groups. At week 52 (defined by LOCF using endpoints prior to discontinuation of IP) the proportions of patients with HbA1c ≤6.5% in the Humalog and LY900014 groups were 12.0% and 11.6%; HbA1c <7% 26.2% and 25.6%; HbA1c ≤8.0 74.2% and 78.9%, and ≤9.0% 94.8% and 96.2%, respectively. Evolution of mean HbA1c was similar between groups over the course of the study (Figure 53).

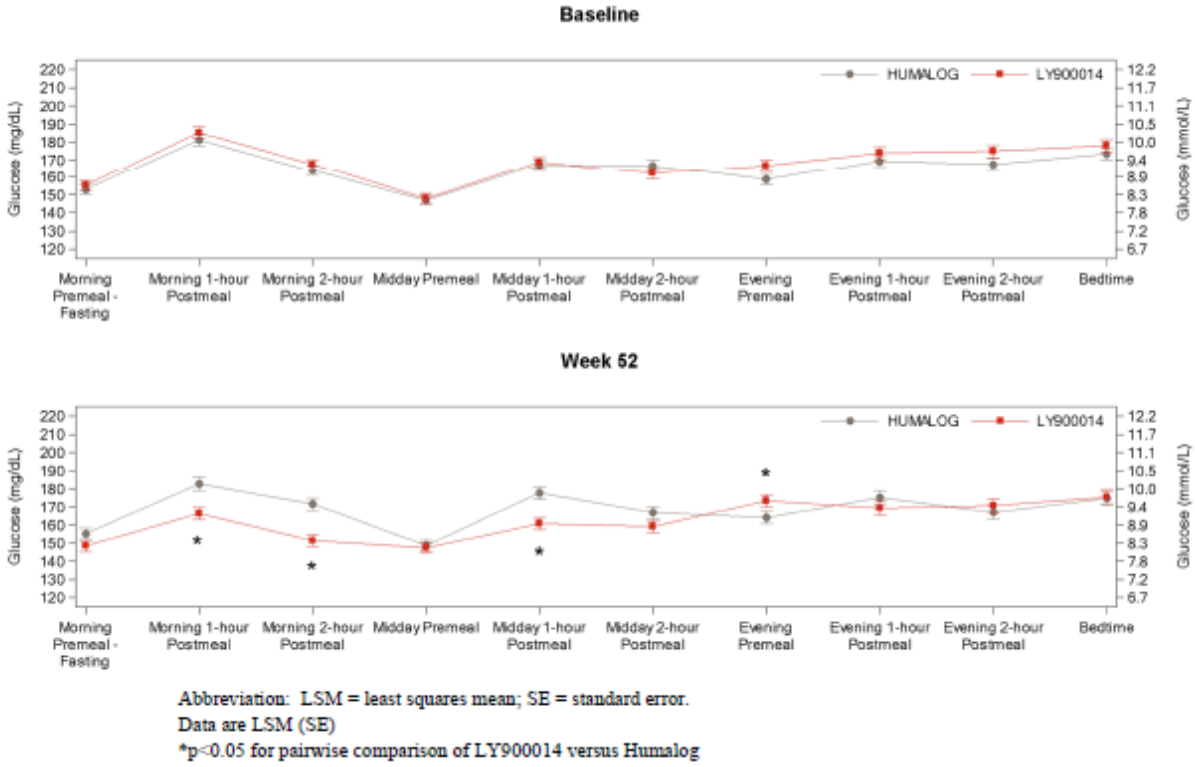
Figure 53. HbA1c from lead-in to Week 52 prior to discontinuation of IP (MMRM), ITRM (T1D)



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 LY900014versus Humalog

At Week 52, LY900014 compared to Humalog was associated with significantly lower SMBG levels at the morning 1- and 2-hour post-meal and the midday 1-hour post-meal time points (Figure 54)

Figure 54. Time course of 10-point SMBG profile at baseline and Week 52 prior to discontinuation of IP. ITRM (T1D)



Abbreviation: LSM = least squares mean; SE = standard error.
Data are LSM (SE)
*p<0.05 for pairwise comparison of LY900014 versus Humalog

LY900014 was overall associated with improved postprandial control compared to Humalog. At Week 52, mean daily post-meal glucose excursions were lower for LY900014 than Humalog

- from premeal to 1 hour postmeal: LSMean difference -0.79 mmol/L (95% CI -1.11, -0.48, p<0.001); and
- from premeal to 2 hours postmeal: LSMean difference -0.46 (95% CI -0.78, -0.15, p=0.004).

No significant treatment differences between the double-blind treatment groups were seen at week 52 in measures of between- or within-day glucose variability, insulin dose (basal, bolus, total, bolus/total ratio) or health outcomes assessments. 1,5-AG levels decreased (worsened) in both treatment groups from Week 26 to Week 52, however, at Week 52, 1,5-AG levels were still statistically significantly higher (better) in the LY900014 group compared to the Humalog group, reflecting better postprandial glucose control in the LY900014 group.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of Efficacy for Pivotal Trial (I8B-MC-ITRM)

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)		
Study Identifier	I8B-MC-ITRM (PRONTO-T1D)	
Design	Phase 3, prospective, randomized, outpatient, multinational, multicenter, 3-treatment group, parallel, treat-to-target, active-controlled study	
	Duration of Lead-in Period:	8 weeks
	Duration of Treatment Period:	26 weeks (primary endpoint, completed) and 52 weeks (ongoing)
	Follow-up Period:	4 weeks
	Duration of anti-insulin lispro antibody follow-up:	26 weeks for eligible patients (ongoing)
	Basal Insulin During the Study	Insulin glargine 100 units/mL, once or twice daily, or Insulin degludec 100 units/mL, once daily
	Treatment Periods: **Lead-In Period**: At the beginning of the lead-in period, patients were switched to an allowed study basal insulin regimen. Basal insulin was titrated during the lead-in period using a titration algorithm to allow the patient to reach the target fasting blood glucose level by the end of this period. All patients were treated with Humalog prior to each meal. **Treatment Period**: At the end of the lead-in period, patients were randomized (4:4:3) to double-blind LY900014 and Humalog, administered 0-2 minutes prior to the start of each meal (mealtime) or open-label LY900014+20 (administered 20 minutes after the start of each meal). During the initial 12 weeks after randomization (intensive titration period), prandial insulin doses were titrated as necessary to meet the target SMBG levels. Basal insulin could be titrated as needed to facilitate optimal prandial dosing or for safety reasons such as hypoglycaemia or unacceptable hyperglycaemia. Thereafter, during the maintenance period (Weeks 12-52 of treatment), it was expected that adjustments to prandial and basal insulin doses would be made to maintain glycaemic control or for safety reasons such as hypoglycaemia or unacceptable hyperglycaemia.	

Summary of Efficacy for Pivotal Trial (I8B-MC-ITRM)

<table>
<tr><td>Hypothesis</td><td colspan="3">The primary objective of this study was to test the hypothesis that LY900014 was noninferior to Humalog on glycaemic control (noninferiority margin [NIM] = 0.4% for HbA1c) in patients with T1D, 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. A NIM of 0.3% was also tested.</td></tr>
<tr><td rowspan="3">Treatment Groups</td><td>LY900014</td><td colspan="2" rowspan="2">Double-Blind Arms: LY900014 or Humalog as a prandial insulin administered 0-2 minutes before the start of the meal (mealtime) in combination with basal insulin (insulin glargine or insulin degludec). Individualized dosing titrated to achieve glycaemic targets.
Randomized: LY900014 (N=451); Humalog (N=442)</td></tr>
<tr><td>Humalog</td></tr>
<tr><td>LY900014+20</td><td colspan="2">Open-Label Arm: LY900014 administered 20 minutes after the start of a meal (postmeal) in combination with basal insulin (insulin glargine or insulin degludec). Individualized dosing titrated to achieve glycaemic targets.
Randomized: LY900014+20 (N=329)</td></tr>
<tr><td rowspan="5">Endpoints And Definitions</td><td rowspan="4">Multiplicity-Adjusted Secondary Endpoints</td><td>Change in HbA1c (%) from baseline to Week 26</td><td>To test the hypothesis that LY900014+20 was noninferior to Humalog on improving glycaemic control (NIM=0.4% for HbA1c) when administered 20 minutes after the start of a meal (LY900014+20) (H5). A NIM of 0.3% was also tested.</td></tr>
<tr><td>1-hour PPG excursion during MMTT at Week 26</td><td>To test the hypothesis that LY900014 was superior to Humalog in controlling 1-hour PPG excursions (H2) (MMTT), when administered as prandial insulin at Week 26.</td></tr>
<tr><td>2-hour PPG excursion during MMTT at Week 26</td><td>To test the hypothesis that LY900014 was superior to Humalog in controlling 2-hour PPG excursions (MMTT), when administered as prandial insulin at Week 26 (H3).</td></tr>
<tr><td>Change in HbA1c (%) from baseline to Week 26</td><td>To test the hypothesis that LY900014 was superior to Humalog on improving glycaemic control when administered as prandial insulin (H4).</td></tr>
<tr><td colspan="2">Other Efficacy Measures</td><td>MMTT, SMBG, Insulin Dose</td></tr>
<tr><td>Database Lock Date</td><td colspan="3">17 September 2018 (26-week treatment period)</td></tr>
</table>

Summary of Efficacy for Pivotal Trial (I8B-MC-ITRM)

Results and Analysis	
Analysis Population and Time Point Description	**Primary Efficacy Analysis and Multiplicity-Adjusted Secondary Objectives** The efficacy estimand included data collected prior to permanent discontinuation of study treatment. The intention-to-treat (ITT) estimand included all data collected regardless of on or off study treatment. The efficacy estimand was the primary estimand for the EU submission. HbA1c: Change from baseline to Week 26; PPG: Week 26
Analysis Description	**Graphical Approach:** 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 multiplicity-adjusted secondary objectives. **Primary Efficacy Analyses**: A mixed model repeated measures (MMRM) analysis of data from all randomized patients, collected prior to permanent discontinuation of investigational product (IP) (efficacy estimand), was used to analyze the primary efficacy measure, change from baseline to Week 26 in HbA1c. The model included the fixed class effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. An unstructured covariance structure was used to model the within-patient errors. Sensitivity analyses, including a per-protocol analysis and multiple imputation methods were also conducted. **Multiplicity-Adjusted Secondary Objectives** included: (H5) noninferiority of LY900014+20 to Humalog for change from baseline in HbA1c (H2) superiority of LY900014 to Humalog for 1 hour MMTT PPG excursion (H3) superiority of LY900014 to Humalog for 2-hour MMTT PPG excursion (H4) superiority of LY900014 to Humalog for change from baseline in HbA1c
Results	**Primary Objective: All Randomized Patients, Efficacy Estimand** The primary objective (H1) was achieved. LY900014 was noninferior to Humalog for glycaemic control. (NIM: 0.4 and 0.3% [4.4 and 3.3 mmol/mol]). • The upper limit of the 95% CI for the difference in change in HbA1c was less than the prespecified noninferiority margin of 0.4%, and less than the noninferiority margin of 0.3%. • LSM difference between treatments (LY900014 minus Humalog) was -0.08% (-0.8 mmol/mol) with a two-sided 95% CI of -0.16% to 0.00 (-1.7 to 0.0 mmol/mol). **Multiplicity-Adjusted Secondary Objectives: All Randomized Patients, Efficacy Estimand** The H5 multiplicity-adjusted secondary objective was achieved. LY900014+20 was noninferior to Humalog for glycaemic control. (NIM: 0.4 and 0.3% [4.4 and 3.3 mmol/mol]). • The upper limit of the 95% CI for the difference in change in HbA1c was less than the prespecified noninferiority margin of 0.4%, and less than the noninferiority margin of 0.3%. • LSM difference between treatments (LY900014+20 minus Humalog) was 0.13% (1.4 mmol/mol) with a two-sided 95% CI of 0.04% to 0.22 (0.5 to 2.4 mmol/mol).

Summary of Efficacy for Pivotal Trial (I8B-MC-ITRM)

<table>
<tr><td rowspan="15">Results (continued)</td><td colspan="5">The H2 and H3 multiplicity-adjusted secondary objectives were achieved. LY900014 was superior to Humalog in controlling 1-hour and 2-hour PPG excursions during MMTT.
• 1-hour: LSM Difference = -27.9 mg/dL (-1.55 mmol/L), p<0.001
• 2-hour: LSM Difference = -31.2 mg/dL [-1.73 mmol/L], p<0.001

The H4 multiplicity adjusted secondary objective was not achieved. LY900014 was not superior to Humalog for glycaemic control.
• LSM Difference = -0.08% (-0.8 mmol/mol); p=0.060

All Randomized Patients, ITT Estimand: From Randomization to Week 26 with Missing Endpoints Imputed by Return to Baseline Multiple Imputation Approach.

In the ITT estimand, multiplicity-adjusted secondary objective H4 was achieved; comparison of LY900014 to Humalog for change from baseline to Week 26 in HbA1c, met statistical superiority.
• LSM difference= -0.08% [-0.90 mmol/mol]; p=0.041)

For the primary objective and all other multiplicity-adjusted secondary objectives, the results were consistent between the efficacy and the ITT estimand.</td></tr>
<tr><td colspan="5">Sensitivity and Per Protocol Analysis
Sensitivity analyses for both the efficacy and ITT estimands, and the per-protocol analyses were consistent with the findings of the primary analyses.</td></tr>
<tr><td colspan="5">Summary and Analysis of HbA1c at Baseline and Week 26
All Randomized Patients, Efficacy Estimand</td></tr>
<tr><td colspan="4">LSM (SE)</td><td>LSM Difference at Week 26</td></tr>
<tr><td>Treatment Group</td><td>Baseline</td><td>Week 26</td><td>Change from Baseline at Week 26</td><td>A: LY900014 vs Humalog (95% CI), p-value
B: LY900014+20 vs Humalog (95% CI), p-value
C: LY900014+20 vs LY900014 (95% CI), p-value</td></tr>
<tr><td colspan="5">HbA1c (mmol/mol)</td></tr>
<tr><td>Humalog</td><td>56.7 (0.34)</td><td>56.1 (0.34)</td><td>-0.6 (0.34)</td><td rowspan="3">A: -0.8 (-1.7, 0.0), p=0.060
B: 1.4 (0.5, 2.4), p=0.003
C: 2.3 (1.3, 3.2), p<0.001</td></tr>
<tr><td>LY900014</td><td>56.7 (0.34)</td><td>55.3 (0.33)</td><td>-1.4 (0.33)</td></tr>
<tr><td>LY900014+20</td><td>56.9 (0.40)</td><td>57.6 (0.39)</td><td>0.8 (0.39)</td></tr>
<tr><td colspan="5">HbA1c (%)</td></tr>
<tr><td>Humalog</td><td>7.33 (0.03)</td><td>7.29 (0.03)</td><td>-0.05 (0.03)</td><td rowspan="3">A: -0.08 (-0.16, 0.00), p=0.060
B: 0.13 (0.04, 0.22), p=0.003
C: 0.21 (0.12, 0.29), p<0.001</td></tr>
<tr><td>LY900014</td><td>7.34 (0.03)</td><td>7.21 (0.03)</td><td>-0.13 (0.03)</td></tr>
<tr><td>LY900014+20</td><td>7.36 (0.04)</td><td>7.42 (0.04)</td><td>0.08 (0.04)</td></tr>
</table>

Summary of Efficacy for Pivotal Trial (I8B-MC-ITRM)

Results (continued)	**Lead-in Period** There was a clinically significant improvement in HbA1c in all treatment groups during the lead-in period designed to optimize basal insulin therapy. From screening to the end of the lead-in period, mean HbA1c decreased from 8.03% (64.27 mmol/mol) to 7.34% (56.74 mmol/mol). **From Baseline to Week 26** **Mealtime LY900014 compared to Mealtime Humalog**: HbA1c decreased from baseline in both treatment groups. Noninferiority was confirmed for HbA1c change from baseline with LY900014 compared to Humalog. **LY900014+20 compared to Mealtime Humalog**: In the multiplicity-adjusted objective H5 (change from baseline in HbA1c), LY900014+20 was non-inferior compared to Humalog. There was an increase in HbA1c within the LY900014+20 treatment group; HbA1c at 26 weeks was modestly but statistically significantly better in the Humalog group. **LY900014+20 compared to Mealtime LY900014**: HbA1c at 26 weeks was modestly but significantly better in the mealtime LY900014 group. Mean HbA1c levels at Week 26 were good in both groups.
	Other Efficacy Measures
	MMTT: Mean PPG Excursions during MMTT, Week 26 (Efficacy Estimand) LY900014 compared to Humalog: Statistically significantly lower PPG excursions with LY900014 at all time points from 15 minutes to 4 hours. LY900014+20 compared to Humalog: Statistically significantly greater PPG excursions up to 1 hour, lower at 3 hours, but similar at 2 and 4 hours. LY900014+20 compared to LY900014: Statistically significantly greater PPG excursion up to 2 hours.
	SMBG: PPG Excursions from Premeal to 1 and 2 hours Postmeal Daily Mean, Week 26 LY900014 compared to Humalog: Statistically significantly lower excursions with LY900014 at both time points. LY900014+20 compared to Humalog: Statistically significantly higher with LY900014+20 from premeal to 1 hour postmeal, with no statistically significant differences at 2 hours. LY900014+20 compared to LY900014: Statistically significantly higher with LY900014+20 at both time points.
	Insulin Dose At Week 26 basal, bolus and total insulin doses were not statistically significantly different between treatments.

Abbreviations: CI = confidence interval; HbA1c = hemoglobin A1c; IP = investigational product; ITT = intent-to-treat; LSM = least squares means;
MMTT = mixed-meal tolerance test; N = number of patients; NIM = noninferiority margin; PPG = postprandial glucose; SE = standard error; SMBG = self-monitored blood glucose; T1D = type 1 diabetes

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J.* 2011;53(6):894–913.

Table 23. Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRM; CGM Substudy)

<table>
<tr><td colspan="4">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)</td></tr>
<tr><td>Study Identifier</td><td colspan="3">I8B-MC-ITRM (PRONTO-T1D) CGM Substudy</td></tr>
<tr><td>Design</td><td colspan="3">This substudy of Study ITRM was conducted at selected sites in participating countries. Blinded CGM was offered to a subgroup of patients in each of the 3 treatment groups.

The Dexcom G4® Platinum System was used for up to 14 days during 2 periods of time, prior to baseline and the 26-week primary endpoint.</td></tr>
<tr><td>Hypothesis</td><td colspan="3">The primary objective of this addendum was to compare double-blind LY900014 and Humalog with respect to the incremental glucose $AUC_{0\text{-}2hours}$ ($iAUC_{0\text{-}2hours}$) after breakfast obtained from up to 14 days of CGM use at Week 26.</td></tr>
<tr><td rowspan="3">Treatment Groups</td><td>LY900014</td><td colspan="2" rowspan="2">Double-Blind Arms: Randomized: LY900014 (N=97); Humalog (N=99)</td></tr>
<tr><td>Humalog</td></tr>
<tr><td>LY900014 +20</td><td colspan="2">Open-Label Arm: Randomized: LY900014+20 (N=73)</td></tr>
<tr><td rowspan="4">Endpoints And Definitions</td><td rowspan="3">Secondary Endpoints</td><td>Incremental glucose $AUC_{0\text{-}2hours}$ after breakfast</td><td>To compare LY900014+20 and Humalog for the following:
• incremental $AUC_{0\text{-}2hours}$ after breakfast</td></tr>
<tr><td rowspan="2">CGM related endpoints</td><td>To compare LY900014, LY900014+20, and Humalog for the following:

Average glucose excursion 0 to 2 hours and 0 to 3 hours and incremental $AUC_{0\text{-}3hours}$ ($iAUC_{0\text{-}3hours}$) after the start of breakfast.</td></tr>
<tr><td>To compare LY900014, LY900014+20, and Humalog for the following:
• duration of time glucose values are within target range (71 to 180 mg/dL [3.9 to 10.0 mmol/L])
• duration of time glucose values are within target range (71 to 140 mg/dL [3.9 to 7.8 mmol/L])
• glucose profile (hourly average glucose and AUC for a 24-hour period; average glucose excursion 0 to 2 hours and 0 to 3 hours and incremental AUC0-3hours ($iAUC_{0\text{-}3hours}$) after the start of breakfast)</td></tr>
<tr><td colspan="2">Other Efficacy Measures</td><td>Other CGM related endpoints</td></tr>
<tr><td>Database Lock Date</td><td colspan="3">17 September 2018 (26-week treatment period)</td></tr>
</table>

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRM; CGM Substudy)

Results and Analysis					
Analysis Population and Time Point Description	All patients in this CGM substudy who were randomized to one of the study treatments, received at least 1 dose of study treatment, and had CGM data from at least 1 collection period (either baseline or endpoint) were included in the analyses of this addendum. The primary outcome measurement was the $iAUC_{0\text{-}2hours}$ after the start of breakfast at Week 26				
Analysis Description	For postprandial glucose (PPG)-related variables, a constrained longitudinal data analysis was performed with type of basal insulin, HbA1c stratum, prandial insulin dosing plan, and treatment as fixed effects, baseline (Visit 8) as a covariate. An unstructured variance-covariance structure was used to model the within-patient errors. For other CGM variables, including time in range, an analysis of covariance (ANCOVA) model with strata and treatment as fixed effects and baseline (Visit 8) as a covariate was used.				
Results	**Primary Objective:** There was a statistically significant treatment difference for $iAUC_{0\text{-}2hours}$ after breakfast demonstrating that LY900014 administered immediately before meals was superior in reducing the $iAUC_{0\text{-}2hours}$ (relative reduction ~51%) when compared to Humalog, and these reductions persisted in comparisons of the $iAUC_{0\text{-}3hours}$ (relative reduction ~70%) and $iAUC_{0\text{-}4hours}$.(relative reduction ~87%)				
	Incremental Area Under the Curve (iAUC) after breakfast, CGM Patient Population, Week 26				
		LSM (SE)			**LSM Difference**
		Mealtime Humalog	**Mealtime LY900014**	**LY900014+20**	**A: LY900014 - Humalog (95% CI), p-value B: LY900014+20 - Humalog (95% CI), p-value C: LY900014+20 - LY900014 (95% CI), p-value**
	mg*h/dL				
	$iAUC_{(0\text{-}2hours)}$	55.3 (10.84)	27.1 (10.83)	45.2 (11.53)	-28.1 (-56.0, -0.3); p=0.048 -10.1 (-38.7, 18.5); p=0.486 18.1 (-10.7, 46.8); p=0.217
	$iAUC_{(0\text{-}3hours)}$	83.9 (19.06)	25.2 (19.30)	52.4 (20.26)	-58.7 (-106.9, -10.5); p=0.017 -31.5 (-81.0, 17.9); p=0.210 27.2 (-22.5, 76.9); p=0.281
	$iAUC_{(0\text{-}4hours)}$	104.1 (27.69)	14.0 (28.07)	37.9 (29.71)	**-**90.1 (-159.5, -20.7); p=0.011 -66.1 (-137.9, 5.6); p=0.071 24.0 (-48.2, 96.2); p=0.513

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRM; CGM Substudy)

	mmol*h/L				
	$iAUC_{(0\text{-}2hours)}$	3.1 (0.60)	1.5 (0.60)	2.5 (0.64)	-1.6 (-3.1, -0.0); p=0.048 -0.6 (-2.1, 1.0); p=0.486 1.0 (-0.6, 2.6); p=0.217
	$iAUC_{(0\text{-}3hours)}$	4.7 (1.06)	1.4 (1.07)	2.9 (1.13)	-3.3 (-5.9, -0.6); p= 0.017 -1.8 (-4.5, 1.0); p=0.210 1.5 (-1.3, 4.3); p= 0.281
	$iAUC_{(0\text{-}4hours)}$	5.8 (1.54)	0.8 (1.56)	2.1 (1.65)	-5.0 (-8.9, -1.1); p= 0.011 -3.7 (-7.7, 0.3); p= 0.071 1.3 (-2.7, 5.3); p=0.513
Results (continued)	**Postmeal iAUC Breakfast and all meals combined at Week 26 (CGM Population)** LY900014 compared to Humalog: Statistically significantly lower for $iAUC_{0\text{-}2hours}$, $_{0\text{-}3hours}$, and $_{0\text{-}4hours}$ for the breakfast meal and for all meals combined. LY900014+20 compared to Humalog: No statistically significant treatment differences in iAUC following the breakfast meal or for all meals combined. LY900014+20 compared to LY900014: No statistically significant treatment differences following the breakfast meal, but LY900014+20 statistically significantly higher for $iAUC_{0\text{-}2hours}$ and $iAUC_{0\text{-}3hours}$ for all meals combined.				
	Average Glucose Excursions following breakfast and all meals combined at Week 26 (CGM Population) (0 to 2 hours and 0 to 3 hours postmeal) LY900014 compared to Humalog: Statistically significantly lower glucose excursions for LY900014 for premeal to 0-2 and 0-3 hours postmeal for breakfast, and all meals combined. LY900014+20 compared to Humalog: No statistically significant treatment differences in glucose excursions from premeal to 0-2 and 0- 3 hours postmeal for breakfast and all meals combined. LY900014+20 compared to LY900014: No statistically significant treatment differences in glucose excursions for 0-2 and 0-3 hours postmeal for breakfast, and for 0-3 hours postmeal for all meals combined. LY900014+20 showed statistically significantly larger glucose excursions from 0-2 hours postmeal for all meals combined.				
	Time in Glucose Target Ranges (Week 26, Daytime; [0600 hours to midnight]) Improvements in PPG control observed with mealtime LY900014 were also associated with a statistically significantly increased time spent in target glucose ranges during the daytime period, the period when prandial insulins are typically used, compared to mealtime Humalog and postmeal LY900014. There were no statistically significant differences for mealtime Humalog versus postmeal LY900014.				

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRM; CGM Substudy)

		Mealtime Humalog	**Mealtime LY900014**	**LY900014+20**	**A: LY900014 - Humalog (95% CI), p-value B: LY900014+20 - Humalog (95% CI), p-value C: LY900014+20 - LY900014 (95% CI), p-value**
Results (continued)	Minutes				
	71 to 180 mg/dL (3.9 to 10.0 mmol/L)	559.4 (17.44)	603.0 (16.38)	554.3 (18.27)	43.6 (6.9, 80.3); p=0.020 -5.1 (-44.1, 33.9); p=0.797 -48.7 (-87.6, -9.8); p=0.014
	71 to 140 mg/dL (3.9 to 7.8 mmol/L)	354.9 (15.61)	395.6 (14.61)	338.6 (16.29)	40.8 (7.9, 73.6); p=0.015 -16.3 (-51.2, 18.7); p=0.360 -57.0 (-91.8,-22.3); p=0.001

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{0\text{-}2hours}$ = AUC from zero to 2 hours; $AUC_{0\text{-}3hours}$ = AUC from zero to 3 hours; CGM = continuous glucose monitoring; CI = confidence interval; h = hours; HbA1c = hemoglobin A1c; iAUC = incremental area under the curve; $iAUC_{0\text{-}2hours}$ = iAUC from time 0 to 2 hours; $iAUC_{0\text{-}3hours}$ = iAUC from time 0 to 3 hours; LSM = least squares means; N = number of patients; PPG = postprandial glucose; SE = standard error; W = week.

Table 24. Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRN)

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)		
Study Identifier	I8B-MC-ITRN (PRONTO-T2D)	
Design	Phase 3, prospective, double-blind, randomized, outpatient, multinational, multicenter, 2-treatment group, parallel, treat-to-target, active-controlled study.	
	Duration of Lead-in Period:	8 weeks
	Duration of Treatment Period:	26 weeks (primary endpoint, completed)
	Follow-up Period:	4 weeks
	Duration of anti-insulin lispro antibody follow-up:	26 weeks for eligible patients (ongoing)
	Basal Insulin During the study	Insulin glargine 100 units/mL once or twice daily, or Insulin degludec 100 units/mL or 200 units/mL once daily
	OAMs during the Study	Patients may have continued the use of up to 2 OAMs (metformin and/or a sodium glucose cotransporter 2 [SGLT-2] inhibitor) during lead-in and treatment periods.
	Treatment Periods: **Lead-In Period**: At the beginning of the lead-in period, patients were switched to an allowed study basal insulin regimen. Basal insulin was titrated during the lead-in period using a titration algorithm to allow the patient to reach the target fasting blood glucose level by the end of this period. All patients were treated with Humalog prior to each meal. **Treatment Period**: At the end of the lead-in period, patients were randomized (1:1) to double-blind treatment with either LY900014 or Humalog (mealtime; 0-2 minutes prior to the start of each meal). During the initial 12 weeks after randomization (intensive titration period), prandial insulin doses were titrated as necessary to meet the target SMBG levels. Basal insulin could be titrated as needed to facilitate optimal prandial dosing or for safety reasons such as hypoglycaemia or unacceptable hyperglycaemia. Thereafter, during the maintenance period (Weeks 12-26 of treatment), it was expected that adjustments to prandial and basal insulin doses would be made to maintain glycaemic control or for safety reasons such as hypoglycaemia or unacceptable hyperglycaemia.	
Hypothesis	The primary objective of this study was to test the hypothesis that LY900014 is noninferior to Humalog on glycaemic control (noninferiority margin [NIM]=0.4% for HbA1c) in patients with T2D, 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. A NIM of 0.3% was also tested.	

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRN)

<table>
<tr><td rowspan="2">Treatment Groups</td><td>LY900014</td><td colspan="2" rowspan="2">Double-Blind Arms: LY900014 or Humalog as a prandial insulin administered 0-2 minutes before the start of the meal (mealtime) in combination with basal insulin (insulin glargine or insulin degludec). Individualized dosing titrated to achieve glycaemic targets.
Randomized: LY900014 (N=336); Humalog (N=337)</td></tr>
<tr><td>Humalog</td></tr>
<tr><td rowspan="4">Endpoints and Definitions</td><td rowspan="3">Multiplicity-Adjusted Secondary Endpoints/ Objectives</td><td>1-hour PPG excursion during MMTT at Week 26</td><td>To test the hypothesis that LY900014 was superior to Humalog in controlling 1-hour PPG excursions (H2) (MMTT), when administered as prandial insulin at Week 26.</td></tr>
<tr><td>2-hour PPG excursion during MMTT at Week 26</td><td>To test the hypothesis that LY900014 was superior to Humalog in controlling 2-hour PPG excursions (MMTT), when administered as prandial insulin at Week 26 (H3).</td></tr>
<tr><td>Change in HbA1c (%) from baseline to Week 26</td><td>To test the hypothesis that LY900014 was superior to Humalog on improving glycaemic control when administered as prandial insulin (change from baseline to Week 26 in HbA1c) (H4).</td></tr>
<tr><td colspan="2">Other Efficacy Measures</td><td>MMTT, SMBG, Insulin Dose</td></tr>
<tr><td>Database Lock</td><td colspan="3">17 August 2018 (26-week treatment period)</td></tr>
<tr><td colspan="4">Results and Analysis</td></tr>
<tr><td>Analysis Population and Time Point Description</td><td colspan="3">Primary Efficacy Analysis and Multiplicity-Adjusted Secondary Objectives
The efficacy estimand included data collected prior to permanent discontinuation of study treatment, and intention-to-treat (ITT) estimand included all data collected regardless of on or off study treatment. The efficacy estimand was the primary estimand for the EU submission.
HbA1c: Change from baseline to Week 26; PPG: Week 26</td></tr>
<tr><td>Analysis Description</td><td colspan="3">Graphical Approach: 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 multiplicity adjusted objectives.

Primary Efficacy Analyses: A mixed model repeated measures (MMRM) analysis of data from all randomized patients, collected prior to permanent discontinuation of investigational product (IP) (efficacy estimand), was used to analyze the primary efficacy measure, change from baseline to Week 26 in HbA1c. The model included the fixed class effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. An unstructured covariance structure was used to model the within-patient errors. Sensitivity analyses, including a per-protocol analysis and multiple imputation methods were also conducted.

Multiplicity-adjusted secondary objectives included:
• (H2) superiority of LY900014 to Humalog for 1 hour MMTT PPG excursion
• (H3) superiority of LY900014 to Humalog for 2-hour MMTT PPG excursion
• (H4) superiority of LY900014 to Humalog for change from baseline in HbA1c</td></tr>
</table>

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRN)

Results

Efficacy Estimand:
The primary objective (H1) was achieved. LY900014 was noninferior to Humalog for glycaemic control. (NIM: 0.4 and 0.3% [4.4 and 3.3 mmol/mol]).

- The upper limit of the 95% CI for the difference in change in HbA1c was less than the prespecified noninferiority margins of 0.4% and 0.3%.
- LSM difference between treatments (LY900014 minus Humalog) was 0.06% (0.6 mmol/mol) with a two-sided 95% CI of -0.05% to 0.16 (-0.6 to 1.8 mmol/mol).

The H2 and H3 multiplicity-adjusted secondary objectives were achieved. LY900014 was superior to Humalog in controlling 1-hour and 2-hour PPG excursions during MMTT in both the efficacy estimand and the ITT estimand.

- 1-hour: LSM difference = -11.8 mg/dL (-0.66 mmol/L), p<0.001
- 2-hour: LSM difference = -17.4 mg/dL (-0.96 mmol/L), p<0.001

The H4 multiplicity-adjusted secondary objective was not achieved. LY900014 was not superior to Humalog for glycaemic control.

- LSM difference = 0.06% (0.6 mmol/mol); p=0.303

ITT Estimand:
The results of the primary objective and all other multiplicity-adjusted secondary objectives were consistent between the efficacy and the ITT estimand.

Sensitivity and Per Protocol Analysis:
Sensitivity analyses for both the efficacy and ITT estimands, and the per-protocol analyses were consistent with the findings of the primary analyses.

Summary and Analysis of HbA1c at Baseline and Week 26 (Efficacy Estimand)

	LSM (SE)			LSM Difference
Treatment Group	**Baseline**	**Week 26**	**Change from Baseline at Week 26**	**LY900014 vs Humalog (95% CI), p-value**
HbA1c (mmol/mol)				
Humalog	56.4 (0.42)	51.5 (0.46)	-4.7 (0.46)	0.6 (-0.6, 1.8); p=0.303
LY900014	56.0 (0.42)	52.1 (0.46)	-4.1 (0.46)	
HbA1c (%)				
Humalog	7.31 (0.04)	6.86 (0.04)	-0.43 (0.04)	0.06 (-0.05, 0.16), p=0.303
LY900014	7.28 (0.04)	6.92 (0.04)	-0.38 (0.04)	

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITRN)

Results (continued)	**Lead-in Period** There was a clinically significant improvement in HbA1c in all treatment groups during the lead-in period designed to optimize basal insulin therapy. From screening to the end of the lead-in period, mean HbA1c overall decreased from 8.3% (67.17 mmol/mol) to 7.3% (56.2 mmol/mol) . **From Baseline to Week 26** HbA1c decreased from baseline in both treatment groups. Noninferiority was confirmed for HbA1c change from baseline with LY900014 compared to Humalog.
	Other Efficacy Measures
	MMTT: Mean PPG Excursions during MMTT, Week 26 (Efficacy Estimand) Statistically significantly lower with LY900014 compared to Humalog, at all time points from 30 minutes to 4 hours.
	SMBG: PPG Excursions from Premeal to 1 and 2 hours Postmeal Daily Mean, Week 26, (LSM Diff, mg/dL [mmol/L]) Statistically significantly lower excursions with LY900014 compared to Humalog, at both time points.
	Insulin Dose Basal, bolus and total insulin doses were similar among study arms at the end of the trial.

Abbreviations: CI = confidence interval; Diff = difference; EU = European Union; HbA1c = hemoglobin A1c; IP = investigational product; ITT = intent-to-treat; LSM = least squares means; MMTT = mixed-meal tolerance test; N = number of patients; MMRM = mixed model repeated measures; NIM = noninferiority margin; OAM = oral antihyperglycaemic medication; PPG = postprandial glucose; SE = standard error; SGLT-2 = sodium glucose cotransporter 2;

SMBG = self-monitored blood glucose; T2D = type 2 diabetes.

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894–913.

Table 25. Summary of Efficacy for the Pivotal Trial (I8B-MC-ITSI)

Title: A Prospective, Randomized, Double-Blind Crossover Comparison Evaluating Compatibility and Safety of LY900014 and Insulin Lispro with an External Continuous Subcutaneous Insulin Infusion System in Adult Patients with Type 1 Diabetes (PRONTO-Pump)		
Study Identifier	I8B-MC-ITSI (PRONTO-Pump)	
Design	Phase 3, prospective, double-blind, randomized, outpatient, multinational, multicenter, 2-treatment, crossover, active-controlled study	
	Duration of Lead-in Period	2 weeks
	Duration of Treatment Period	12 weeks; 2-period crossover (two 6-week treatment periods, no washout between)
	Follow-up Period	4 weeks
	Treatment Periods: **Lead-In Period**: At the beginning of the lead-in period, all patients were transferred to Humalog. Patients must have been using the MiniMed 530G, MiniMed 630G (US) or 640G (EU) insulin pump, and the bolus speed for all pumps was set to standard speed (1.5 U/min) for the duration of the lead-in and treatment phases of the study. Dexcom G5, with standard, manufacturer-specified alerts and alarm features enabled, was used by all patients in real-time mode beginning at Visit 2 and continuing throughout the treatment phase of the study. **Treatment Period**: At randomization, patients were randomly assigned to 1 of 2 double-blind treatment sequences in a 1:1 ratio: LY900014/Humalog and Humalog/LY900014. Patients crossed-over to the alternate treatment at Week 6. Patients on the study were required to change their infusion set every 72 ± 4 hours, unless a change was required earlier due to failure of the infusion set.	

Hypothesis	The primary objective was to confirm the compatibility and safety of LY900014 and Humalog when delivered by CSII with the secondary/tertiary objectives of evaluating short-term efficacy in terms of glycaemic control as measured by change from baseline in HbA1c and by CGM related end-points, including iAUC and time in target ranges.
Treatment Groups	Double-blind, crossover design, LY900014 or Humalog administered via CSII. Mealtime boluses were administered 0-2 minutes before the start of the meal, with basal infusion rates throughout 24 hours a day, with correction boluses as necessary. Individualized dosing titrated to achieve glycaemic targets. Randomized: LY900014/Humalog (N=24); Humalog/LY900014 (N=25)

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITSI)

Endpoints and Definitions	Tertiary Objective	HbA1c, actual and change from baseline to Week 6	To separately evaluate the glycaemic control of LY900014 and Humalog using summary statistics of actual and change from baseline to Week 6 in HbA1c for each treatment
	Tertiary Objective	CGM related end-points	To compare LY900014 and Humalog with respect to: • incremental area under the glucose versus time curve from 0 to 1 hour ($iAUC_{0\text{-}1hour}$) after breakfast, obtained from CGM use • duration (minutes) and percentage of time glucose values were within the target range (71 and 180 mg/dL [3.9 and 10.0 mmol/L]), obtained from CGM use • duration (minutes) and percentage of time glucose values were within the target range (71 and 140 mg/dL [3.9 and 7.8 mmol/L]), obtained from CGM use • glucose profiles, based on 24-hour interstitial glucose obtained from CGM use
	Other Efficacy Measures		Other CGM related endpoints, Insulin Dose
Database Lock	07 September 2018		
Results and Analysis			
Analysis Population and Time Point Description	HbA1c reflects patients' blood glucose control over the past 2-3 months and therefore there may be potential carryover effect from Period I to Period II. For this reason, only Period I results are discussed for treatment comparisons, to assess the observed trend in HbA1c. CGM analyses were conducted on the CGM Population that included all randomized patients who received at least 1 dose of the randomly assigned IP and had CGM data from at least 1 collection period (lead-in, Period I and Period II). For the CGM-related endpoints, treatment comparisons were based upon the derived outcome variables using the CGM data collected for 4-6 weeks.		
Analysis Description	**Efficacy and CGM Analysis** Treatment comparisons for the primary objective were performed using the Wilcoxon signed-rank test at the full significance level of 0.05, with patients who were dosed in both treatment periods. No multiplicity adjustment was made for secondary and tertiary objectives. A restricted maximum likelihood based, mixed-effect model repeated measures (MMRM) analysis was used to analyze continuous longitudinal CGM variables. The model included the fixed class effects of treatment, period, sequence, strata, and the continuous, fixed covariate of baseline value.		

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITSI)

Results

HbA1c

All patients entered the study under good glycaemic control, which was further improved in Period I (first 6 weeks of study treatment) and was maintained throughout Period II.

In Period I, both treatments showed statistically significant reductions from baseline. The LY900014 treatment had a numerically greater reduction in mean HbA1c, even though LY900014 started with a lower baseline (Baseline, % [mmol/mol]: LY900014: 6.97 [52.68]; Humalog: 7.17 [54.89]).

Period I Mean Change from baseline, % [mmol/mol]:
LY900014: -0.39 [-4.23], 95% CI: (-0.55, -0.22 [-6.03,-2.43])
Humalog: -0.25% [-2.78], 95% CI: (-0.42, -0.09 [-4.55,-1.00])

CGM: Incremental Post breakfast AUC (iAUC) CGM Population, Weeks 4-6

There was a trend toward better glycaemic control post-breakfast (lower $iAUC_{0\text{-}1hour}$ and $iAUC_{0\text{-}2hours}$) for LY900014 compared with Humalog.

Treatment Group	LSM (SE)		LSM Difference
	Humalog	LY900014	LY900014 - Humalog (95% CI), p-value
mg*h/dL			
$iAUC_{0\text{-}1hour}$	21.79 (3.31)	16.59 (3.35)	-5.19 (-12.58, 2.19); p= 0.159
$iAUC_{0\text{-}2hours}$	56.95 (9.15)	44.32 (9.26)	-12.64 (-33.43, 8.16); p= 0.222
mmol*h/L			
$iAUC_{0\text{-}1hour}$	1.21 (0.18)	0.92 (0.19)	-0.29 (-0.70, 0.12); p= 0.159
$iAUC_{0\text{-}2hours}$	3.16 (0.51)	2.46 (0.52)	-0.70 (-1.86, 0.45); p= 0.222

CGM: Time with Glucose in Target Ranges, Daytime, Nighttime and 24-hour periods

There were no statistically significant treatment differences in the mean duration of time in any of the target ranges for daytime, nighttime, and 24-hour period, but there was a trend towards more time with glucose in the target ranges during the daytime and 24-hour periods for LY900014-treated patients, but not during nighttime.

- 71-180 mg/dL (3.9 to 10.0 mmol/L)
  - Daytime (LSM): LY900014, 717.62 minutes; Humalog, 686.46 minutes
  - 24-hour (LSM): LY900014, 946.01 minutes; Humalog, 906.77 minutes
- 71-140 mg/dL (3.9 to 7.8 mmol/L)

	○ Daytime (LSM): LY900014, 482.09 minutes; Humalog, 451.45 minutes ○ 24-hour (LSM): LY900014, 632.87 minutes; Humalog, 601.26 minutes

Summary of Efficacy for the Pivotal Trial (I8B-MC-ITSI)

Results (continued)	**CGM: Time with Glucose in Hyperglycaemic Ranges** There were no statistically significant treatment differences in the mean duration of time in any of the hyperglycaemic ranges for daytime, nighttime, and 24-hour period for Weeks 4 to 6, but there were trends towards less time with glucose in hyperglycaemic ranges for LY900014-treated patients during daytime and 24-hour period, but not during nighttime.
	Pump Factors The changes from baseline to Week 6 for pump factors of breakfast carbohydrate ratio, active insulin time, breakfast insulin sensitivity factor, and frequency of use of non-normal bolus type were small, and similar between treatments; actual values at Week 6 were also similar between treatments.
	Insulin Dose There were no statistically significant treatment differences for basal, bolus, or total insulin dose, at Week 6.

Abbreviations: AUC = area under the concentration versus time curve; CGM = continuous glucose monitoring; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA1c = hemoglobin A1c; iAUC = incremental area under the curve; $iAUC_{0\text{-}1hour}$ = iAUC from time 0 to 1 hour; $iAUC_{0\text{-}2hours}$ = iAUC from time 0 to 2 hours; LSM = least squares means; N = number of patients; OUS = outside the United States; SE = standard error; US = United States.

Analysis performed across trials (pooled analyses and meta-analysis)

Sensitivity analyses were conducted on the primary endpoint (change in HbA1c from baseline to Week 26) and secondary endpoint (1h and 2h glucose excursions during MMTT) in ITRM and ITRN. Missing-at-random (MAR) analyses were conducted. Primary analysis model was also repeated using the per protocol and completer populations. The sensitivity analyses supported non-inferiority of LY900014 vs. Humalog on overall glycaemic control as measured by HbA1c level and superiority of LY900014 to Humalog in controlling 1-hour and 2-hour PPG excursions during mixed meal tolerance test (data not included in this AR).

Subgroup analyses were performed in ITRM and ITRN from baseline to endpoint. The change in HbA1c from baseline to the primary endpoint (Week 26) for various subgroups was analysed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit, and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 26) was evaluated to assess the treatment by subgroup interaction.

The analysed subgroups are listed in Table 26.

One statistically significant (p=0.084) treatment-by-subgroup interaction was observed in the subgroup analyses of ITRM (T1D): Subgroup of baseline 2-hour PPG at baseline ≤10/mmol/L and 10/mmol/L. The 95% CIs for both PPG subgroups led to the same conclusion in non-inferiority.

In the subgroup analyses of ITRN (T2D), there was a statistically significant difference in treatment by subgroup interaction at Week 26 based on MMRM for the subgroup of baseline HbA1c (≤8.0% and 8.0%). The magnitude of treatment difference at Week 26 was smaller in the baseline HbA1c ≤8.0% category than in the baseline HbA1c >8.0% category although the 95% CIs for both categories included zero. There was also a significant difference in the treatment by subgroup interaction for the subgroup of body mass index (BMI<35 kg/m2 vs.≥35 kg/m2). The treatment difference showed an increase in HbA1c in the baseline BMI <35 kg/m2 category but showed a decrease in the baseline BMI ≥35 kg/m2 category.

Although the directions of LSM difference were different, the 95% CI for both BMI categories led to the same conclusion in non-inferiority.

As a conclusion on subgroup analyses, consistent treatment effects across subgroup analyses were observed in comparison of LY900014 with Humalog based on patient characteristics, diabetes characteristics and geographic areas, with the three exceptions described by the Applicant. Statistically significant differences in glycaemic response were seen in T1D subjects (in the subgroup divided by baseline 2-hour PPG at baseline ≤10 mmol/L vs. >10 mmol/L) and in T2D subjects (in the subgroup of baseline HbA1c at ≤ 8.0% and >8.0% and the subgroup of BMI at <35 kg/m2 and ≥35 kg/m2); at the significance level of 0.1. The noted treatment-by-subgroup interactions are not considered clinically relevant.

Table 26. Subgroup Analyses of HbA1c in Studies ITRM (T1D) and ITRN (T2D)

	Study ITRM	Study ITRN
Age	<40, ≥40 years	<65, ≥65 years
Baseline 1-hour PPG (≤180, >180 mg/dL)	Yes	Yes
Baseline 1-hour PPG Excursion	Yes	Yes
Baseline 2-hour PPG (≤180, >180 mg/dL)	Yes	Yes
Baseline 2-hour PPG Excursion	Yes	Yes
Baseline HbA1c Stratum	≤7.5%, >7%	≤8%, >8%
Body Mass Index	<25 vs ≥25 kg/m^2	<25 vs ≥25 kg/m^2
	<30 vs ≥30 kg/m^2	<30 vs ≥30 kg/m^2
	No	<35 vs ≥35 kg/m^2
Country	Yes	Yes
Duration of Diabetes	Yes	Yes
Ethnicity	Yes	Yes
Personal CGM/FGM Use During the Study (Yes, No)	Yes	No
Prandial Insulin Dosing Plan	Yes	No
Number of Prandial Doses at Study Entry (<3, ≥3)	No	Yes
Race	Yes	Yes
Region	Yes	Yes
Sex (Male, Female)	Yes	Yes
Type of Basal Insulin During the Lead-in Period	Yes	Yes
SGLT-2 inhibitor treatment	No	Yes

Abbreviations: CGM = continuous glucose monitoring; FGM = flash glucose monitoring; HbA1c = hemoglobin A1c; No = subgroup analysis not conducted; PPG = postprandial glucose; SGLT-2 = sodium-glucose cotransporter-2; Yes = subgroup analysis conducted.

Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy results were not pooled. Pooling of T1D and T2D studies for efficacy analyses would not have been appropriate due to quite distinct nature of T1D and T2D.

Clinical studies in special populations

The Applicant has not conducted PK studies on LY900014 in subjects with hepatic or renal impairment. This approach was accepted in the EMA scientific advice (EMA/CHMP/SAWP/400498/2016). It was agreed with the Applicant that no systemic effect by treprostinil was expected due to very low systemic concentrations, and lispro insulin *per se* is a well-known substance.

A paediatric patient PK/PD (I8B-MC-ITSA) comparing Humalog versus LY900014 in children and adolescents (6 to <18 years) with T1D is ongoing. A Phase 3 trial (I8BMC-ITSB) is planned for 2019. The Applicant states that an indication for children will be submitted once both trials are completed.

The Applicant submitted upon request tabulated data for confirmation of consistency of the treatment effect and safety profile included in clinical studies during development of LY90014. The summary tables by age group (<65, ≥65 to <75, ≥75 to <85 and ≥85) were provided separately for studies ITRM and ITRN (tables not included here for brevity). As there were only 3/49 randomised patients aged above 65 years in ITSI, these patients were not included in the analyses. No patients above the age of 85 were included in the Phase 3 studies, and the number of patients aged above 75 years was very low.

Of all randomised patients, there were 407 subjects aged <65, 30 subjects aged ≥65 to <75, 5 subjects aged ≥75 to<85 years and none ≥85 years of age.

In Study ITRM, there were fewer patients ≥65 years of age (n=98 [8%]) than patients <65 years of age (n=1124 [92%]). HbA1c after 26 weeks of treatment was similar between age groups above and below 65 years of age (Humalog: 7.3%; LY900014: 7.2%); but numerically higher in patients ≥75 years of age (Humalog: 7.7%; LY900014: 7.5%). The 1- and 2- hour PPG response was similar between the age groups of LY900014 treated patients, but larger PPG excursions were noted among patients >65 to 75 years of age treated with Humalog. All documented hypoglycaemia <3.0 mmol/L was similar between age groups above and below 65 years of age for Humalog treated patients (~13.3 events per patient/year [EPY]); however, the rate in LY900014 treated patients was numerically higher in patients ≤65 years of age (13.1 EPY) than in LY900014 treated patients >65 to 75 years of age (5.5 EPY) or ≥75 years of age (3.6 EPY). Due to the imbalance in sample size between patients above and below 65 years of age, these observations should be interpreted with some caution since higher HbA1c and reduced hypoglycaemia risk observed in older patients may also be influenced by a more conservative approach to diabetes management.

In Study ITRN, there were 194 subjects <65, 133 subjects ≥65 to <75, and 10 subjects ≥75 to <85 years of age. Over 26 weeks of treatment, mean HbA1c was reflected good average glycaemic control in subjects aged <65, ≥65 to <75, and ≥75 years with LY900014 (6.9%, 6.8% and 6.6%, respectively) and Humalog (7.0%, 6.8%, and 7.1%, respectively). The PPG excursions at 1 hour after meal were in the age groups <65, ≥65 to <75, and ≥75 years 3.9, 3.7, and 2.6 mmol/L in the Humalog and 4.0, 4.0, and 4.0 mmol/L in the LY900014 group, respectively. At 2 hours, the PPG excursions were 5.2, 5.2 and 4.1 mmol/L in the Humalog group, and 3.3, 3.1, and 3.4 mmol/L in the LY900014 group in age groups <65, ≥65 to <75, and ≥75 years, respectively. Hence, the numerical improvement in PPG excursions with LY900014 vs. Humalog was seen only at 2 hours post-meal in T2D patients; without any effect on overall glycaemic control. However, the variation in the PPG results was large in older age groups.

Documented hypoglycaemia <3.0 mmol/L rates were overall were similar between treatments and tended to be lower or similar in older patients compared with patients < 65 year of age.

Supportive study(ies)

The LY900014 KwikPen internal mechanisms and industrial design are based on existing KwikPen platforms and thus, the human factors development programme focused on the design for differentiation (KwikPen and carton design). During development of the LY900014 pre-filled KwikPens, the Applicant conducted two formative human evaluation studies and subsequent human factor (HF) validation study.

The two formative human evaluation studies (HF study 3/2017, HF study 6/2017) included a total of 48 participants and based on the study results, a single LY900014 label strategy was chosen. All in all, the studies did not reveal potential differentiation problems among representative users. No changes to the colour pattern of the pen or carton were needed based on the formative studies.

The purpose of the human factor validation study was to demonstrate that the intended users can differentiate the LY900014 KwikPens when presented in a group of products similar in appearance and

function. The human factor validation study was conducted in simulating conditions of actual use and consisted of 66 participants (17 paediatric, 8 adult patients, 7 adult caregivers, 15 nurses, 15 pharmacists, and 4 colour-blind consumers without diabetes). The products (pens or cartons) used as distractors in the differentiation scenarios included five currently authorized meal-time insulins and five basal insulins. Based on the results, in 192 out of 198 scenarios, participants successfully completed all 3 differentiation scenarios with no use errors or problems. There was a total of 6 instances (from 5 participants, all aged from 10 to 13 years) in which participants did not successfully complete a scenario. The five paediatric participants experienced difficulties to distinguish the pens, especially to differentiate the three LY900014 KwikPen variants. In general, the LY900014 100 units/mL KwikPen and LY900014 200 units/mL KwikPen have quite similar appearance (same pen body colour and shape, blue-white label etc.). As highlighted in the guideline "Risk minimisation strategy for high-strength and fixed-combination insulin products" the potential mix-up between the insulin pens is an important aspect that should be thoroughly assessed during the product development. In the end, also children should be able to distinguish between the pens since paediatric development is ongoing for LY900014. However, it is not expected that a child would have access to different kinds of bolus insulin. The important issue is to distinguish between bolus and basal insulin and in this regard, no errors occurred even among children. None of the adults made any errors, including nurses and pharmacists that might handle insulin pens of different patients. It is acknowledged that as the pens yield units (instead of volumes), mixing pens with the two different strengths would not affect the actually given insulin dose. Therefore, the similarity of the colour scheme of the LY900014 KwikPens with 100 and 200 U/mL is not expected to cause unacceptable hazard.

2.5.3. Discussion on clinical efficacy

LY900014 has been developed as a faster-acting prandial insulin for subcutaneous (SC) use and for intravenous (IV) use to improve glycaemic control in patients with type 1 diabetes mellitus (T1D) or type 2 diabetes mellitus (T2D). Currently the application is intended for use in adults; however, paediatric development is ongoing. The aim has been to provide a faster glucose-lowering effect, which mimics more closely the physiological mealtime insulin response than the currently available insulin lispro with the global trade names Humalog and Liprolog (duplicate licence), without compromising the safety. On the EU market there is also Insulin lispro Sanofi, a biosimilar lispro insulin. Humalog was approved in the EU in 1996.

Faster insulin time-action profile and earlier glucose lowering effect has been attained by two excipients with independent mechanisms to accelerate the absorption of insulin lispro from the site of injection or infusion: treprostinil and sodium citrate. A microdose of treprostinil enhances absorption of insulin lispro through increased local vasodilatation, however with negligible systemic exposure. Sodium citrate speeds absorption of insulin by enhancing local vascular permeability.

One purpose with LY900014 has been to develop a prandial insulin that would allow for post-meal dosing in situations when dosing immediately before the meal is not suitable or possible, in addition to dosing prior to meal ingestion.

Design and conduct of clinical studies

Scientific advice has been obtained for the overall development plan (EMA/CHMP/SAWP/400498/2016) and the Applicant has followed the advice. As the active substance insulin lispro has been on market since 1996, omission of Phase 2 studies can be accepted. The PK/PD studies have confirmed that the overall hypoglycaemic effect of LY900014 is similar to Humalog regardless of the faster onset of glucose-lowering action of LY900014. The CHMP also agreed on omission of separate studies on patients with hepatic or renal insufficiency and interaction studies. Patients with moderate to severe renal insufficiency or

significant hepatic impairment were excluded from the Phase 3 studies, and very few subjects with any renal or hepatic impairment were enrolled. No relevant difference in treatment response was observed between subjects below and above 65 years of age; however, few subjects were above age 75 years and none above 85 years in the Phase 3 studies.

The efficacy evaluation of LY900014 is based on three Phase 3 studies comparing LY900014 with Humalog. Studies ITRM (T1D) and ITRN (T2D) were randomized, parallel-design, double-blind, active controlled, treat-to-target trials that evaluated the safety and efficacy of LY900014 when administered as a prandial insulin as part of a MDI regimen in adult patients with T1D and T2D, respectively. Study ITSI was a 2-treatment, 2-period (6-week treatment each) crossover design trial that evaluated the safety and compatibility of LY900014 in the treatment of patients with T1D when administered via CSII compared with Humalog.

The choice of Humalog as comparator was supported by the CHMP during SA and is considered appropriate. As LY90014 is a new faster-acting formulation of lispro insulin by the MAH of Humalog, demonstrating significant differences in safety and efficacy of LY900014 compared with Humalog is the best approach to assess any benefit of LY900014 in addition to the insulin products already on market.

A total of 421 healthy subjects and 342 patients with T1D or T2D were exposed to LY900014 in the 22 completed clinical pharmacology trials. Altogether 1944 patients with T1D or T2D received study drug (LY900014 or the active comparator Humalog) in the Phase 3 studies, of which 1165 received LY900014.

The inclusion and exclusion criteria of the Phase 3 studies are considered acceptable. Patients were excluded if there were safety issues (with labile diabetes control such as frequent hypoglycaemic events or ketoacidosis requiring emergency treatment, and of patients with hypoglycaemia unawareness) or inappropriate combination of medications in T2D patients (GLP1 receptor agonists, pramlintide or thiazolidinediones). The inclusion and exclusion criteria allowed for participation of typical diabetes patients representative of the target patient population.

Both ITRM (T1D) and ITRN (T2D) trials included an 8-week lead-in period; a 12-week intensive titration period; and a 26-week controlled period assessing non-inferiority based on change in HbA1c of LY900014 compared with Humalog (primary objective). ITRM was conducted with three arms: LY900014 and Humalog administered immediately (0-2 minutes) prior to each meal in a double-blind manner, and as third treatment group LY900014 was administered 20 minutes after the start of a meal (LY900014+20) open-label, as it was not possible to blind this treatment group with different injection timing. The non-inferiority margin (NIM) was 0.4 according to FDA's requirements, however, for the EU, also non-inferiority with the NIM 0.3 has been calculated as part of primary endpoint. ITRM included a long-term maintenance period of 26 weeks (up to 52 weeks from initiation of treatment period), in addition to the lead-in period (8 weeks) and controlled treatment period (26 weeks). Results were originally submitted for up to the end of the controlled treatment period up to 26 weeks. The 52-week efficacy data submitted with the D121 responses confirmed the 26-week findings. No difference was seen in overall glycaemic control reflected by HbA1c between Humalog and LY900014. However, lower glucose excursions from premeal to 1 hour and 2 hour post-meal time points at Week 52 for LY900014 than Humalog, and larger decrease from baseline to Week 52 in glucose excursions from premeal to 1-hour and 2-hour time points post-meal was observed for the LY900014 group compared with the Humalog group.

ITRM (T1D) also contained a continuous subcutaneous glucose monitoring (CGM) blinded substudy with 269 patients who received at least 1 dose of study treatment and wore the CGM device during at least 1 collection period (either baseline or post baseline) (LY900014, 97; Humalog, 99; LY900014+20, 73) that has been finalised.

ITRN (T2D) compared LY900014 and Humalog, both administered immediately prior to meal. The ITRN study on T2D patients contained no long-term maintenance period.

The primary endpoint of studies ITRM(T1D) and ITRN(T2D) was non-inferiority of LY900014 vs. Humalog in achieving glycaemic control as measured by HbA1c. This endpoint was assessed at 26 weeks, which included 12-week intensive titration period followed by a maintenance period. At the initiation of the 8-week lead-in period in these studies (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 100 units/mL or insulin degludec were transferred to an allowed study basal regimen of insulin glargine 100 units/mL once or twice daily or insulin degludec 100 units/mL or 200 units/mL once daily. At Visit 8, initiation of the controlled treatment period, patients were randomized to either mealtime (0-2 minutes before the start of the meal) Humalog or mealtime LY900014 and continued their basal insulin regimen.

Notably the studies were treat-to-target studies with intensive titration algorithms for achieving good glycaemic control. Consequently, there was a marked improvement in glycaemic control in both studies already during the lead-in period (the so-called "trial effect"). In this kind of setting superiority is difficult to show as insulin can always be individually titrated to achieve desired glucose levels. Furthermore, if the insulin regimen causes e.g. hypoglycaemic events between meals, this can be controlled by optimised snacking. Hence, non-inferiority is an appropriate goal for the primary endpoint, which was glycaemic control. The choice of the primary endpoint is in accordance with the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (14 May 2012. CPMP/EWP/1080/00 Rev. 1).

However, as the difference between LY900014 and Humalog is in postprandial control, the clinically most important efficacy endpoints are the multiple measures of postprandial control collected as secondary or tertiary endpoints. The methods for collection of postprandial and diurnal glucose fluctuations included 4-hour standardized mixed-meal tolerance tests (MMTT) at baseline and at 26 weeks of treatment, self-monitoring of blood glucose (SMBG), samples for fasting glucose, and additionally in the ITRM substudy and ITSI, continuous glucose monitoring (CGM) and flash glucose monitoring (FGM). 1,5-anhydroglucitol (1,5-AG) was determined as a measure of postprandial glycaemia that has been implicated to be associated with diabetic complications.

The primary endpoint of the ITRM CGM Substudy was to compare double-blind LY900014 and Humalog with respect to the $iAUC_{0\text{-}2hrs}$ after breakfast obtained from up to 14 days of CGM use at Week 26. Multiple other measures of glucose variability were assessed as secondary and tertiary endpoints.

The ITSI study on patients with T1D using continuous subcutaneous insulin infusion (CSII) via external insulin pump was primarily designed to confirm safety and compatibility of LY900014 for use in an insulin pump. The study was not powered to demonstrate non-inferiority or superiority for efficacy. However, multiple endpoints were collected also for assessment of efficacy.

The phase 3 clinical trials were overall conducted in an acceptable way. In studies ITRM (T1D) and ITRN (T2D), the PPG excursions were measured from randomisation to primary endpoint at 26 weeks only twice: at baseline and week 26. Based on the description, only subjects with data on both time points are included in the analysis, thus both estimates estimate rather efficacy estimand than ITT estimand. As the primary aim of the analysis of PPG excursion was to demonstrate superiority, the ITT estimand is of primary interest. Further to CHMP request, the Applicant conducted a new analysis using multiple imputation with baseline as a reference to provide a more conservative estimate of the treatment effect at week 26 for both PPG excursion endpoints, and results of this analysis were comparable with original results.

Efficacy data and additional analyses

In all phase 3 studies, the study populations were representative for the target population and well balanced between study groups with regards to demographic and disease characteristics. The proportion of EU-patients vs. non-EU-patients in the Phase 3 studies were adequate: in the ITRM (T1D), 667/1316 (50.7%); in the ITRN (T2D), 234/750 (31.2%) and in ITSI (T1D, CSII) 31/49 (63.3%).

Of patients who were entered in the lead-in period, 94/1316 discontinued the study before randomisation in the ITRM (T1D) and 213/963 in the ITRN (T2D); most commonly due to withdrawal by subject, physician decision or lost-to-follow-up. After randomisation, drop-out rates were overall small and balanced between study arms. In ITRM, 18/442 subjects in the Humalog arm, 8/451 in the LY900014 arm and 11/329 in the LY900014+20 arm of the study discontinued before entering in the safety follow-up period or long-term maintenance period. In the ITRN (T2D), 18/337 in the Humalog and 16/336 in the LY900014 arm discontinued after randomisation. In the ITSI (T1D, CSII), 3/49 discontinued: one due to protocol violation, 2 due to withdrawal by patient.

At the beginning of the 8-week lead-in periods of ITRM (T1D) and ITRN (T2D) all patients were changed to use Humalog as prandial insulin and either insulin glargine or insulin degludec as basal insulin. A marked improvement in overall glycaemic control achieved by optimisation of the multiple-dose regimen was seen in both studies during the lead in-period: In ITRM (T1D), the mean HbA1c decreased from 8.03% to 7.34% and in ITRN (T2D) from 8.3% to 7.3%. Consequently, most patients started the randomised treatment period already in good glycaemic control.

Results on HbA1c

The primary endpoint in both multiple daily injection studies, ITRM in T1D subjects and ITRN in T2D subjects, was to test the hypothesis that LY900014 was noninferior to Humalog on glycaemic control, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec. Glycaemic control was measured by change in HbA1c from baseline to 26 weeks using a noninferiority margin (NIM) of 0.4%. Additionally, a NIM of 0.3 as calculated to fulfil the EU requirements. Both LY900014 and Humalog were injected at the start of a meal (mealtime; 0 to 2 minutes prior to the start of the meal). Efficacy results were calculated as efficacy estimand including data collected prior to permanent discontinuation of IP and for the ITT estimand including all data collected, regardless of IP use. Post-meal dosing was included in Study ITRM (T1D) as an open-label arm (LY900014+20) to support a post-meal dosing indication.

Secondary multiplicity adjusted objectives included the following objective regarding HbA1c: testing the hypothesis that LY900014 is at 26 weeks superior to Humalog in improving glycaemic control, when administered as prandial insulin, and noninferior to Humalog in improving glycaemic control, when administered 20 minutes after the start of a meal.

The primary endpoint was met in both ITRM (T1D) and ITRN (T2D): LY900014 was noninferior to Humalog on glycaemic control, when administered as prandial insulin, for both the NIM of 0.4% and NIM of 0.3%. For the assessment of non-inferiority, results on analyses according to ITT estimand (including all data collected through Week 26, regardless of IP use) and the efficacy estimand (including data collected prior to discontinuation of IP through Week 26) are considered important. In ITRM (T1D), from a similar baseline HbA1c level, the change in HbA1c at week 26 was −0.05 and −0.13 %-units for Humalog and LY900014, respectively (efficacy estimand); corresponding figures for the ITT estimand were −0.09and −0.18 %-units for Humalog and LY900014, respectively. In ITRN (T2D), the LSM change in HbA1c was −0.43% in the Humalog group and −0.38% in the LY900014 group; LY900014 vs. Humalog LSM Difference (95% CI) was 0.06 (-0.05, 0.16) (efficacy estimand). The corresponding figures for the ITT estimand of the LSM change in HbA1c in ITRN (T2D) were −0.46% in the Humalog group, −0.43% in the LY900014 group; p=0.624. There were no statistically significant treatment differences at any time

point during the lead-in and treatment periods. The sensitivity analyses (tipping point and per protocol analyses) for the efficacy and ITT estimands supported the findings of the primary analyses in both studies.

Multiplicity-adjusted secondary endpoints on HbA1c included superiority of LY900014 to Humalog (ITRM, T1D, ITRN, T2D) and noninferiority of LY900014+20 to Humalog (ITRM, T1D). Non-inferiority of LY900014+20 to Humalog in terms of change in HbA1c was met in ITRM (T1D) with LSM difference in HbA1c of 0.14% with a two-sided 95% CI of 0.053% to 0.226 (ITT estimand). The secondary endpoint of superiority of prandial LY900014 vs. prandial Humalog for improving glycaemic control (change from baseline to Week 26 in HbA1c) was met for the efficacy estimand but not for the ITT estimand in the ITRM study. In ITRN (T2D), neither the efficacy nor the ITT estimand showed superiority of LY900014 vs. Humalog. It is of importance for interpretation of these results that both ITRM and ITRN were treat-to-target studies with intensive titration algorithms for achieving good glycaemic control. Consequently, a marked improvement in HbA1c occurred in both studies already during the lead-in period, and the controlled treatment periods of the study started already in good glycaemic control. In this kind of setting superiority is difficult to show as the insulin doses are individually and meticulously titrated to achieve desired glucose levels. Furthermore, if the insulin regimen causes hypoglycaemic events between meals, this can be controlled by optimised snacking. Hence, non-inferiority on glycaemic control was an appropriate goal for the primary endpoint. The choice of the primary endpoint is also in accordance with the "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (14 May 2012. CPMP/EWP/1080/00 Rev. 1). Postprandial glycaemia accounts for only about 50% of overall diurnal glycaemia while the rest is from fasting glycaemia. Hence, the lowering of PPG excursions by even a clinically relevant amount as was seen in ITRM and ITRN is only a fraction of postprandial excursion and even a smaller fraction of overall glycaemia.

The proportions of T1D patients achieving the HbA1c targets ≤6.5 % and <7 % in the LY900014 and Humalog groups at Week 26 were similar in ITRM, at ~16% and ~35%, respectively. In the LY900014+20 group, the proportions achieving these HbA1c targets were lower: ~10% and ~26%, respectively. In ITRN in T2D, the proportions of patients achieving the HbA1c targets ≤6.5% and <7.0% at Week 26 were similar for LY900014 and Humalog, at approximately 37% and approximately 55%, respectively. These results support injecting LY900014 prior to meal instead of post-meal, whenever possible. Nevertheless, the results on noninferiority of LY900014+20 to Humalog (Humalog thus given prior to meal) in terms of change in HbA1c in ITRM support including the possibility of postprandial administration in the indication, similar to the indication of Humalog. The Phase 3 program includes no comparison of post-meal LY900014 and post-meal Humalog, which might have favoured LY900014 more in comparison with Humalog. On the other hand, there was no comparison in the Phase 3 studies of LY900014 with Humalog that would have been injected 15 minutes prior to meal, which is recommendable if feasible. Such a comparison might have attenuated the benefit achieved by LY900014.

Results on glucose variability

The major difference between LY900014 and Humalog is seen in postprandial control, hence, the clinically most important efficacy endpoints are the multiple measures of postprandial control collected as secondary or tertiary endpoints. The methods for collection of postprandial and diurnal glucose fluctuations included 4-hour standardized mixed-meal tolerance tests (MMTT) at baseline and at 26 weeks of treatment, self-monitoring of blood glucose (SMBG), samples for fasting glucose, and additionally in the ITRM (T1D) substudy and ITSI, continuous glucose monitoring (CGM) and flash glucose monitoring (FGM). 1,5-anhydroglucitol (AIG) was determined as a measure of postprandial glycaemia that has been implicated to be associated with diabetic complications.

The primary endpoint of the ITRM (T1D) CGM Substudy was to compare double-blind LY900014 and Humalog with respect to the $iAUC_{0\text{-}2hrs}$ after breakfast obtained from up to 14 days of CGM use at Week 26. Multiple other measures of glucose variability were assessed as secondary and tertiary endpoints. The ITSI study on patients with T1D using continuous subcutaneous insulin infusion (CSII) via external insulin pump was primarily designed to confirm safety and compatibility of LY900014 for use in an insulin pump. The study was not powered to demonstrate non-inferiority or superiority for efficacy. However, multiple endpoints were collected also for assessment of efficacy.

Of note, ITT results on glycaemic control are especially important for estimating the effect of the product on overall glycaemic control as a risk factor for long-term complications of diabetes. For the efficacy table and especially for the product information, results based on efficacy estimand are more relevant, as treating physicians and patients need to know the effects of LY900014 after injection during therapy. ITT results that are diluted by patients who discontinued treatment are not relevant in the clinical setting when insulin is used for replacement of endogenous insulin secretion.

The multiplicity adjusted efficacy endpoints of superiority of LY900014 to Humalog in controlling 1-hour and 2-hour PPG excursions were met, when administered as prandial insulin in the MMTT at Week 26. In ITRM (T1D), the observed differences in mean PPG excursions, (ITT estimand) were 1.53 mmol/L (95% CI [−1.94, −1.13], p<0.001) less at 1 hour and 1.69 mmol/L (95% CI [−2.24, −1.14], p<0.001) less at 2 hours after meal in the LY900014 arm in comparison with the Humalog arm of the study. The respective mean differences in PPG excursions based on efficacy estimand were 1.55 mmol/L (95% CI [−1.96, −1.14], p<0.001) less at 1 hour and 1.73 mmol/L (95% CI [−2.28, −1.18], p<0.001) less at 2 hours after meal. For T2D subjects in the ITRN (T2D), the respective LSM differences for 1 hour and 2-hour PPG excursions were −0.67 (95% CI [−1.01, −0.32, p<0.001) mmol/L and −0.98 mmol/L (95% CI [−1.41, −0.54], p<0.001) (ITT estimand) and −0.66 (95% CI [−1.01, −0.30], p<0.001) mmol/L and −0.96 mmol/L (95% CI [−1.41, −0.52], p<0.001) (efficacy estimand). The observed differences in the 1-hour and 2-hour PPG excursions were in both studies highly statistically significant (p<0.001 for all comparisons). As T1D patients have total insulin deficiency and are more insulin-sensitive and leaner than T2D patients are, it is not surprising that the improvement in PPG was larger in ITRM (T1D) than in ITRN (T2D). In T2D, remaining endogenous insulin secretion reacts to circulating glucose levels, which attenuates glycaemic fluctuations. Furthermore, thicker subcutaneous tissue is expected to delay absorption of LY900014, whereas insulin resistance impairs glucose uptake in muscles and enhances hepatic glucose production. Therefore, the achieved hypoglycaemic effect by the ultra-rapid LY900014 in comparison with Humalog is larger in T1D than T2D. Nevertheless, in T2D patients, the lowering of PPG was almost 1 mmol/L at 2 hours post-meal, which could be considered clinically relevant, too. The reduction of 1.69 mmol/L in the 2-hour PPG in T1D is deemed clinically highly relevant. In conclusion, a significant difference in efficacy between LY900014 and Humalog has been demonstrated, in the context of falling outside of the scope of Article 82 (1) of Regulation EC No 726/2004 (duplicate MA); this has been a prerequisite for a separate stand-alone MA for LY900014, as it has the same active substance (insulin lispro) as within Humalog. Health outcome analyses showed no difference between treatment arms and clinical outcome endpoints were not investigated. The applicant was requested to discuss which patients with T1D and T2D are expected to benefit from LY900014 given its faster onset of action compared with currently marketed insulin lispro products. The applicant provided more data on the effects of LY900014 on postprandial glycaemic control in comparison with other mealtime insulins and concluded that LY900014 has a favourable benefit/risk profile in patients with T1D and T2D. In clinical practice, however, it is expected that LY900014 would preferentially be used for patients who cannot reach their individual glycaemic goals due to inadequately controlled glucose excursions after meals.

Post-meal dosing was not tested in Study ITRN (T2D) but was tested in T2D patients in two clinical pharmacology studies (Studies ITRH and ITRW). In ITRH, each T2D patient was randomized to 1 of 6 treatment sequences comprising single SC doses of LY900014 and lispro insulin (a reference

formulation prepared by diluting commercially available Humalog with sterile diluent for Humalog to adjust the concentration of insulin lispro to 95 IU/mL, thereby matching the concentration of insulin lispro in LY900014) administered at different times (−15 minutes, 0 minutes [immediately before meal], and +15 minutes) relative to the start of a test meal. LY900014 reduced the PPG excursion during the MMTT compared with the reference formulation of lispro insulin for each of the meal-to-dose timing intervals. In ITRW, LY900014 showed a trend towards an earlier glucose-lowering effect and a lower postprandial glucose excursion over the complete 5-hour MMTT compared to Humalog at both of the meal-to-dose timing intervals (immediately before the start of the test meal and 20 minutes following the start of the test meal). Consequently, studies ITRH and ITRW support extrapolation of the beneficial effects of LY900014 also when given after the meal on post-meal glucose levels to T2D patients in addition to T1D patients.

In ITRM (T1D), fasting glucose (FG) median (LS Mean) values at week 26 in the MMTT were 7.20 (7.41), 6.58 (6.98), and 6.40 (7.02) mmol/L in the Humalog, LY900014, and LY900014+20 groups, respectively. In pairwise comparison, the LSM difference between LY900014 vs. Humalog was −0.43 mmol/L (95% CI [−0.75, −0.12] p=0.007) and between LY900014+20 and Humalog, −0.39 mmol/L ([−0.74, −0.04], p=0.029). These differences in FG at Week 26 in favour of LY900014 vs. Humalog and LY900014+20 vs. Humalog were not expected, as the duration effect of the prandial insulin prior to evening snack does not extend to following morning. The finding might be speculated to be due to lower postprandial excursion after evening snack in the previous evening that is still reflected in the morning glucose level. No difference in FG was observed between LY900014 and Humalog groups in T2D patients (ITRN).

Incremental Area Under the Serum Glucose Concentration Time Curve (iAUC) during MMTT was determined in both ITRM (T1D) and ITRN (T2D) based on samples collected in the MMTT up to 2 hours post-meal. In both studies, iAUC was statistically significantly lower with LY900014 than with Humalog during the 4-hour test at Week 26. In ITRM, iAUC was statistically significantly higher in LY900014+20 versus LY900014 during the 4-hour test at Week 26.

The primary objective of the ITRM (T1D) CGM substudy was to compare double-blind LY900014 and Humalog with respect to the iAUC0-2hrs after breakfast obtained from up to 14 days of CGM use at Week 26. In the substudy, LY900014 significantly reduced the $iAUC_{0\text{-}2hrs}$ after breakfast at Week 26 when compared to Humalog (relative reduction ~51%) and significant reductions continued for comparisons of $iAUC_{0\text{-}3hrs}$ (relative reduction ~70%) and $iAUC_{0\text{-}4hrs}$ (relative reduction ~87%). The ambulatory glucose profiles obtained in the ITRM CGM substudy show similar improvement in PPG control after lunch and dinner. In ITSI (T1D, CSII), similar trend for lower iAUC for LY900014-treated patients was seen, however ITSI was not powered to show statistical differences in efficacy endpoints. The results on iAUC are considered to highlight the clinical importance of achieved improvement in postprandial control more robustly than point measures at 1 and 2 hours post-meal.

The ITSI (T1D, CSII) contained a summary and analysis of duration of time (percentage and minutes) in glucose target ranges for daytime, night time, post-breakfast, and 24-hour periods. Target ranges analysed were 3.9 to 10.0 mmol/L, 3.9 to 7.8 mmol/L, and ≤10.0 mmol/L. No statistically significant treatment differences in the mean duration of time in any of the target ranges for daytime, night time, and 24-hour period were seen; only a trend towards more time with glucose in the target ranges during the daytime and 24-hour periods for LY900014-treated patients. However, in the better-powered ITRM (T1D) substudy, time in range [3.9 to 10.0 mmol/L] at week 26 was 43.6 minutes more and in range [3.9 to 7.8 mmol/L] 40.8 minutes more during daytime in the LY900014 group vs. Humalog. No statistically significant differences were seen between LY90014+20 vs. Humalog. However, patients in the LY900014+20 group were significantly less time in range than patients in the LY900014 group. Time in hyperglycaemia (>10 mmol/L) was not different between LY900014 and Humalog. The LY900014+20 group had ~20 minutes longer time in hyperglycaemia during night time in comparison with Humalog; and furthermore, ~63 minutes more time in hyperglycaemia during daytime and ~75 minutes more

during the 24-hour period in comparison with LY900014 group. These results strengthen the conclusion that injecting LY900014 post-meal may be an alternative to Humalog premeal (and Humalog post-meal), but the best option is to inject LY900014 premeal, if feasible.

Samples were collected in all three Phase 3 studies for determination of 1,5-anhydroglucitol (1,5-AG) levels in plasma, a marker of short-term glucose control and treatment response, especially postprandial hyperglycaemia. Low levels of circulating 1,5-AG have been implicated to be useful as predictor for micro- and macrovascular events and even mortality of diabetic patients (Selvin et al 2014, Selvin et al 2016, Shiga et al). However, the data are mostly from retrospective databases, and no long-term trial data are available on this matter. In the ITRM (T1D), 1,5-AG levels improved (increased) in the LY900014 group and decreased in the Humalog and LY900014+20 groups, and at Week 26 the LSM difference was statistically significant in favour of LY900014 vs. both other groups. In the ITNR (T2D) and ITSI (T1D, CSII), however, no difference was seen between study arms. The Applicant discussed that several factors might have confounded the results on 1,5-AG in the ITRN study, including variable dietary intake, a potential non-linear relationship between glycaemia and 1,5-AG, especially near the renal threshold, the biological variability in renal threshold for glucose reabsorption, potential confounding by SGLT2 inhibitor use in ITRN, and the different degrees of glycaemic control achieved between studies. At Week 52, the HbA1c values and proportions of subjects meeting HbA1c targets were similar in the LY900014 and Humalog groups. Postprandial glucose excursions were significantly lower with LY900014 than Humalog through-out the study and also at 52 weeks.

Health outcome measures in the ITRM (T1D) and ITRN (T2D) showed no clinically relevant differences between groups.

Subgroup analyses were conducted in studies ITRM (T1D) and ITRN (T2) for multiple demographic and disease characteristics. In study ITSI, there were no subgroup analyses for HbA1c because efficacy was not a primary objective.

Subgroup analyses demonstrate consistent treatment effects across all subgroup analyses with three exceptions. Statistically significant differences in glycaemic response were seen in one subgroup of T1D subjects, divided by baseline 2-hour PPG at baseline ≤10 mmol/L vs. >10 mmol/L (p= 0.084). The 95% CIs for both PPG subgroups led to the same conclusion in noninferiority. In T2D subjects, two subgroups had a statistically significant treatment-by-subgroup interaction based on MMRM: the subgroup of baseline HbA1c at ≤8.0% and >8.0% (p=0.017) and the subgroup of BMI at <35 kg/m2 and ≥35 kg/m^2 (p=0.058). The number of patients in the HbA1c >8.0% subgroup (LY, n=46; Humalog, n=44) was small compared to the HbA1c ≤8.0% subgroup (LY900014, n=270; Humalog, n=276). The 95% CIs for both BMI categories led to the same conclusion in noninferiority. These findings are not unexpected. In patients with worse glycaemic control, there is more room for improvement, which may explain the larger difference in efficacy achieved by LY900014 vs. Humalog in patients with higher HbA1c. In more obese patients, on the other hand, the relative benefit by enhanced absorption of LY900014 vs. Humalog could be reduced due to the thicker subcutaneous tissue that does not allow speedy absorption. The noted treatment-by-subgroup interactions are not considered clinically relevant. Results of all other subgroup analyses were consistent with the primary analysis.

Human factor (HF) studies were performed by the Applicant. The first tested two proposed label patterns and two proposed colour palettes. No differentiation failures were noted. The second study was conducted to evaluate the three pen designs (KwikPen 100 units/mL, KwikPen 200 units/mL, and Junior KwikPen) for differentiation against themselves and other insulin pen products in order to determine readiness to proceed to HF validation testing. No errors were made by the 61 adult participants (adult patient/caregiver, nurse, pharmacist, or colour-blind consumer). However, five paediatric participants aged 10 to 13 experienced difficulties in distinguishing the pens, especially in differentiation of the three LY900014 KwikPen variants. The Applicant was asked to justify the colours of the prefilled pens and

packages. The Applicant referred to low reporting rates of medication errors in the EU across all Humalog KwikPen types/strengths, ranging from 0.01% to 0.02%. In the end, also children should be able to distinguish between the pens since paediatric development is ongoing for LY900014. It is, however, not expected that a child with diabetes would have access to different kinds of bolus insulins. Furthermore, as the pens yield units (instead of volumes), mixing pens with the two different strengths would not affect the insulin dose actually given. As a conclusion, the similarity of the colour scheme of the LY900014 KwikPens with 100 and 200 U/mL and KwikPen Junior is not expected to cause unacceptable hazard.

The Applicant was requested to justify the KwikPen Junior presentation in this application that concerns only adults. It is noted that the Junior KwikPen is suitable for also adult patients who may benefit from finer insulin dose adjustment by steps of 0.5 units. The Applicant proposes a new design for the Liumjev 100 units/mL Junior KwikPen outer carton and label mock-ups, which is less likely to give the impression that the pen was intended to be used for paediatric patients. The new design is deemed acceptable. The Applicant also proposes to add on the carton of the pen the sentence "For adults use only" to decrease the possible risk of off-label use in children and adolescents. This sentence is not considered efficient in the prevention of prescribing errors; this could have promotional connotations and moreover, the inclusion of additional non-statutory text may impair the readability of other important elements of the packaging. Therefore, the sentence is requested to be omitted from the carton.

The Applicant also submitted preliminary, scarce data from ongoing paediatric studies on LY900014: ITSA, a PK/PD study, and ITSB, a clinical efficacy/safety trial. The initial results show a faster PK/PD profile in children and adolescents administered LY9000014 than Humalog.

The Applicant prefers to keep the name Liumjev KwikPen Junior to retain consistency between the names of the Liumjev and Humalog pens. The Humalog KwikPen Junior also yields insulin in increments of 0.5 units, and it might create confusion if adult subjects using Humalog KwikPen Junior were transitioned to using Liumjev KwikPen Junior, if the latter was named differently. This appears reasonable and is acknowledged. Based on the preliminary information submitted by the Applicant, the incidence and timing of hypoglycaemia in paediatric patients is not yet available. Some differences in at least timing of hypoglycaemia are expected in paediatric vs. adult patients. Since larger difference in postprandial glucose lowering between Lumjev and Humalog have been showed in children than in adults, it is possible that paediatric patients may experience more incidences of hypoglycaemia.

As all aforementioned may still have an impact on medication errors, as well as on the safety of paediatric patients, the MAH is requested to monitor, analyse and report potential for medication errors and off-label use in the paediatric population linked to adverse reactions for Liumjev as part of the upcoming PSUSA for insulin lispro (covering all formulations for Humalog, Liprolog and (soon) Liumjev). Based on the analysis of the reported data as part of the upcoming PSUSA, the MAH should also discuss/propose whether further risk minimisation measure(s) are considered necessary at this stage.

The results on HbA1c and post-meal glucose excursions are given according to the efficacy estimand analyses in the proposed Product Information. This is considered acceptable, as for the treating physician and for the patient it is important to know what is expected when LY900014 is injected – hence, the result on only patients using the product, without those who discontinued, is valuable for treatment decisions.

2.5.4. Conclusions on the clinical efficacy

Non-inferiority of LY900014 vs. Humalog in overall glycaemia (HbA1c) was demonstrated in T1D and T2D. The data from the clinical trials show that the shorter time-action profile of LY900014 in comparison with Humalog translates into statistically and clinically relevant differences in postprandial glycaemic control. The difference is larger in T1DM, but is considered to be clinically relevant also in T2D. Furthermore, analyses on time-in-range and incremental AUC of postprandial glucose concentration strongly support

the clinically relevant difference between LY900014 and Humalog on postprandial control. Taking in account that the Phase 3 trials ITRM in T1D and ITRN in T2D were conducted according to the treat-to-target principle, no marked differences in overall glycaemic control were expected. However, in T1D, the achieved HbA1c was slightly (but not clinically relevantly) better with LY900014 than Humalog at Week 26. During the long-term maintenance period of ITRM, the difference in HbA1c between LY900014 and Humalog decreased and was no more significant at week 52.

The results obtained by several different methods measuring glucose fluctuations during mixed-meal tolerance test, self-monitoring of glucose, and continuous and flash glucose monitoring indicate that LY900014 should optimally be injected prior to meal to achieve improvement in postprandial glycaemia compared with Humalog. However, if dosing prior to meal is not feasible, post-meal dosing is possible and results in comparable glycaemic excursions as achieved with premeal Humalog.

2.6. Clinical safety

The active substance insulin lispro is known for more than 20 years. The present MAA concerns use in adults only. Paediatric development is, however, ongoing for LY900014.

A new excipient, treprostinil, is present in the product. Treprostinil (a prostacyclin analogue) has a marketing authorisation for the treatment of pulmonary arterial hypertension in some EU member states. In comparison with treprostinil concentrations in PAH patients, both the Cmax as the AUC(0-24h) obtained after SC or IV administration of LY900014 were more than 1000-fold lower (after IV administration of a 15U dose of LY900014, mean treprostinil Cmax was ~0.0275 ng/ml and AUC(0-tlast) was 0.0017 ng*h/ml – even when an anticipated maximum IV dose of 40U or a continuous IV infusion of 30 U/h is administrated, treprostinil concentrations would be either non-detectable or transient detectable up to 10 minutes post-injection). In addition, the clinical treprostinil AUC(0-24h) exposure in LY900014 is 460-fold to 9100-fold lower than the no observed adverse effect level (NOAEL) AUC(0-24h) exposure of treprostinil in the rat, rabbit, or dog toxicology studies. Therefore, no clinically relevant systemic exposure is expected of treprostinil following SC or IV administration of LY900014 doses used in clinical practice. Due to the negligible systemic exposure following SC and IV administration of LY900014, the safety of treprostinil per se has not been included in the safety assessment.

No integrated safety database including both clinical pharmacology trials and Phase 3 trials was included in the submission. The Applicant integrated safety data from the Phase 3 MDI studies ITRM (T1D) and ITRN (T2D) except for hypoglycaemia and immunogenicity. Data from LY900014 and LY900014+20 were pooled as one treatment group (All LY) for comparison with Humalog. The integrated database includes data from the 26-week treatment period of the MDI studies. The 52-week safety data from ITRM and part of 4-week safety extension data from ITRN were submitted with the D121 response. In addition, the safety and compatibility of LY900014 and Humalog administered via CSII was assessed based on the Phase 3 Study ITSI. Due to differences in the method of administration and design, data from Study ITSI was not integrated with the Phase 3 MDI studies.

For the integrated MDI studies, two sets of analyses were conducted for many safety parameters (TEAEs, serious adverse events [SAEs], vital signs, subgroup analyses):1) analyses with available data regardless of treatment status and 2) analyses with data while the patient was on study drug.

The Applicant also submitted integrated safety data from clinical pharmacology studies. In total, the Applicant had performed 22 clinical pharmacology studies (in addition to 3 phase 3 studies). Of these, 6 studies did not contribute to the integrated safety data: ITRA (treprostinil with insulin lispro vs Humalog in 28 heathy), ITRJ (LY900014 formulation vs Humalog in 24 healthy), ITRE (LY900014 vs Humalog in 23 healthy), ITRH (LY900014 vs Humalog in 30 T2D), ITRG (LY900014 vs Humalog in 30 T1D), and ITRP

(LY900014 in 24 healthy). The Applicant adequately clarified the selection criteria of studies in the pooled analyses and provided safety data for several individual pharmacology studies upon request.

Currently the combined data from the integrated clinical pharmacology studies evaluating exposure, demographics, disposition, adverse events, hypoglycaemic events, injection site reactions, immunogenicity, clinical laboratory evaluations, and cardiovascular safety are integrated only from 7 studies that used the final LY900014 commercial formulation and included Humalog as the comparator.

In clinical pharmacology studies, the results of patients with T1D and T2D were combined. The Applicant was requested to present the results for the T1D and T2D patients separately as e.g. for hypoglycaemia and immunology the events are dependent on diabetes type. The additional analyses performed by the Applicant yielded results consistent with the results of the Phase 3 studies.

Depending on the nature of the safety data, different statistical methods have been applied in the analyses. The methods as such are acceptable, however, the statistical analysis of the safety data is not controlled for type I error rate, nor are the studies powered for demonstration of differences, thus the low p-values can be only considered as indicative of potential treatment difference, and similarly higher p-value may indicate no difference or lack of power to detect difference.

Patient exposure

A total of 1165 patients received LY900014 in the three Phase 3 studies: ITRM, ITRN and ITSI. Of these patients, 921 received LY900014 as multiple daily injections for at least 180 days, and 33 received LY900014 via pump for at least 42 days. In clinical pharmacology studies, a total of 294 subjects (74 healthy subjects and 220 patients with T1D or T2D) received at least 1 dose of study drug (either LY900014 or Humalog).

A total of 431.6 patient-years (PY) was gathered for preprandial LY900014 and 182.5 PY for postprandially administered LY900014 in the ITRM study (T1D, MDI regimen, 52-week CSR). For CSII treatment, 5.6 PY were gathered in the ITSI study (T1D). In the ITRN study (T2D, MDI regimen), 164.0 PY were gathered for preprandial LY900014.

Differences in characteristics between T1D and T2D patients were typical (this could be assessed in phase III studies).

Of the three pivotal studies, The ITSI study was the only study primarily for safety. It was designed to compare LY900014 and Humalog with respect to the rate of continuous subcutaneous insulin infusion (CSII) set failures that led to premature infusion set changes due to a pump occlusion alarm or due to unexplained hyperglycaemia.

Adverse events

Table 27 presents an overview on the AEs in the Phase 3 MDI studies. In the Phase 3 MDI studies (integrated safety database), the proportion of subjects with TEAEs was 57.3% in the Humalog group and 58.1% in the LY900014 group. TEAEs reported in at least 5% of patients were nasopharyngitis and upper respiratory tract infection, reported at similar frequencies between treatment groups.

Table 27. Overview of AEs, integrated 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)	3	(0.3)	5	(0.3)	1.20	0.490	0.837
Serious Adverse Events	66	(8.5)	86	(7.7)	152	(8.0)	0.89	0.615	0.511
Discontinuations from Study due to an Adverse Event	3	(0.4)	5	(0.4)	8	(0.4)	1.36	0.852	0.672
Discontinuations from Study Treatment due to an Adverse Event	8	(1.0)	16	(1.4)	24	(1.3)	1.42	0.519	0.416
Treatment-emergent Adverse Events	446	(57.3)	648	(58.1)	1094	(57.7)	1.05	0.631	0.631
Treatment-emergent Adverse Events Related to Study Treatment*c	38	(4.9)	70	(6.3)	108	(5.7)	1.22	0.715	0.339

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
*e - Heterogeneity of odds ratios across studies was assessed using the Breslow Day test
*f - p-values are from Cochran-Mantel-Haenszel (CMH) test of general association stratified by study.

In the integrated clinical pharmacology studies, TEAEs of all causalities (all subjects) occurred in 68/290 (23.4%) in the LY900014 group and 64/289 (22.1%) in the Humalog group. The proportions of subjects with TEAEs between LY900014 and Humalog were in the same order of magnitude also in the subpopulations comprising healthy (41.1% vs. 38.4%) and diabetic (17.5% vs. 16.7%) subjects.

Study ITSI

The ITSI study was primarily intended to support use of LY900014 for continuous subcutaneous insulin infusion (insulin pump) for T1D patients (N=49). The primary objective was comparison of LY900014 and Humalog with respect to the rate of infusion set failures that led to premature infusion set changes due to a pump occlusion alarm or due to unexplained hyperglycaemia with blood glucose (SMBG >13.9 mmol/L that did not decrease within 1 hour following a correction bolus delivered via the pump). No difference was seen between study arms, as 2 subjects in the LY900014 arm had two infusion set failures and 4 subjects in the Humalog arm had 4 infusion set failures.

In ITSI, the TEAEs (all and related to study drug) were more than twice as common in the LY900014 arm than in the Humalog arm. This difference was driven by infusion site reactions (see separate chapter regarding injection and infusion site reactions).

Serious adverse event/deaths/other significant events

In Study ITSI, the overall incidence of SAEs was low. Two patients (LY900014, 1 [2.0%]; Humalog, 1 [2.1%]) reported SAEs, both were events of hypoglycaemia. No deaths occurred in ITSI.

There were ten death events in studies ITRM (T1D) and ITRN (T2D). Five deaths occurred from randomization to safety follow-up and prior to database lock (All LY, 3; Humalog, 2). Five additional deaths (All LY, 4; Humalog, 1) were reported in Studies ITRM and ITRN as of 31 December 2018, including 4 deaths (All LY, 3; Humalog, 1) reported after the safety follow-up visit and after the database lock, and 1 death reported after the primary endpoint cut-off in Study ITRM (LY900014+20). There were no deaths in Study ITSI (T1D, CSII).

None of the 10 deaths were considered by the investigator to be related to study drug.

The most common SAEs in ITRM, ITRN and ITSI were hypoglycaemia SAEs.

In ITRM T1D patients, no differences in severe hypoglycaemic events were seen between the study groups. The narrow MedDRA preferred term search, or survey of rate and incidence of severe post-meal hypoglycaemia at different time points did not change the result (See also Section "Hypoglycaemic events").

During the 26 weeks in ITRN, no difference in hypoglycaemia SAEs in T2D at any time points was seen. With regard to the potential severe hypoglycaemia events, only one patient had reported to have hypoglycaemic shock (See also Section "Hypoglycaemic events").

In ITSI study in T1D patients, there was one hypoglycaemia SAE in both groups and severe hypoglycaemia rates and incidences were similar in both study arms.

In Study ITRR, a patient experienced a SAE of hypoglycaemia approximately 6 days after LY900014 administration, which resulted in study discontinuation. The patient had switched to pre-study therapy (insulin aspart administered by CSII) 6 days prior to the event.

Two SAEs of severe hypoglycaemia events were reported in studies evaluating insulin pump safety. The events were considered not related to study treatment.

Even though the reporting rates of hypoglycaemic events as SAE were not different between LY900014 and Humalog, differences in incidence, rates, and timing of hypoglycaemic events were seen in the collected results from MMTTs, CGM, and SMBG, as described below under subtitle "Hypoglycaemic events".

Injection and infusion site reactions and hypersensitivity

In phase 3 studies, injection/infusion site reaction TEAEs (pain, itching, induration, erythema, oedema) were remarkably more common in the LY900014 group compared to the Humalog group: 30 (2.7%) vs 1(0.1%) in ITRM and ITRN, and 19(38.8%) vs 6 (12.5%) in ITSI, respectively.

In the integrated clinical pharmacology studies, injection site reactions occurred in 20/290 (6.9%) in the LY900014 group and 7/289 (2.4%) in the LY900014 group.

Further, for ITSI the Applicant reported that infusion site reaction evaluation showed that "Most events of infusion site pain and infusion site induration were reported by a single Spanish site (50/62 for pain; 18/20 for induration)." The Applicant explained that in the Spanish sites, the same infusion site reactions were reported by multiple channels: either spontaneous adverse event reporting or via the eDiary as the reason for an unplanned infusion set change, but as a unique AE, a practice that differs from standard AE reporting. Furthermore, the same infusion site reactions from different anatomical sites of infusion were counted as separate events. In all, 58 events of infusion site pain and 19 events of infusion site induration were reported by both Spanish sites.

No between-group differences in other treatment-emergent hypersensitivity reactions were seen in Phase 3 studies. In clinical pharmacology studies, only few patients reported pain, and the events and the magnitude were equally divided between the study groups.

According to injection site assessments in studies evaluating treprostinil, treprostinil concentration did not appear to be in relation to injection site reactions, nor did sodium citrate. There were, however, between-group differences highlighting injection site reactions in subjects/patients both in PK and phase 3 studies. The Applicant discussed that both local vasodilation by treprostinil and enhanced permeability by citrate, together with irritation caused by these excipients per se may be behind this difference. All injection site reactions were mild or moderate and resolved without sequalae.

From long-term safety data of the ITRM study, over the course of the study from randomisation to safety follow-up, more patients in the LY900014 (3.3%) and LY900014+20 (2.4%) groups experienced ≥1 injection site reaction TEAEs compared to the Humalog group (0.9%). The mechanism behind the increased incidence of injection site reactions with LY900014 in comparison with Humalog is not known for certain. The Applicant discusses that the local vasodilatation by treprostinil and enhanced permeability by sodium citrate could both be partly responsible for this difference; or these compounds could *per se* cause the irritation. Treprostinil is known to cause injection site reactions when administered in higher doses as a vasodilatory drug; and citrate has been associated with injection site pain in other injectable products. Nevertheless, the injection site reactions were mild or moderate in severity, resolved without sequalae and did not lead to treatment discontinuation through Week 52.

Hypoglycaemic events

To be noted, the Applicant has applied different statistical comparisons in the safety analysis. The methods as such are acceptable, however, the statistical analysis of the safety data is not controlled for type I error rate, nor are the studies powered for demonstration of differences, thus the low p-values can be only considered as indicative of potential treatment difference, and similarly higher p-value may indicate no difference or lack of power to detect difference.

T1D

Study ITRM (T1D, MDI)

There were 65 subjects with severe hypoglycaemic events in the 26-week period of ITRM: LY900014, n=25 (5.5%), Humalog, n=25 (5.7%), LY900014+20, n=15 (4.6%). The narrow MedDRA preferred term search, or survey of rate and incidence of severe post-meal hypoglycaemia at different time points did not change the result.

The rate and incidence of all documented hypoglycaemia was similar in the Humalog group and the LY900014+20 group, and slightly lower in the LY900014 group than in the other groups (incidence presented in Table 28). The incidence and rate of non-nocturnal hypoglycaemic events was slightly higher (both with BG <3.0 mmol/L and <3.9 mmol/L) when LY900014 was injected postprandially instead of preprandially (i.e., in the LY900014+20 group vs. the LY900014 group).

Table 28. Incidence of hypoglycaemia from randomization to week 26 prior to discontinuation of study drug (ITRM safety population)

Category/Subcategory of Hypoglycemia	Humalog (N=442)	LY900014 (N=451)	LY900014+20 (N=329)	p-value[a,b]	p-value[a,c]	p-value[a,d]
BG ≤70 mg/dL, (3.9 mmol/L)						
Documented symptomatic hypoglycemia						
Patients with hypoglycemia, n (%)	404 (91.40)	414 (91.80)	293 (89.06)	0.833	0.272	0.194
Number of events	13137	12818	9657			
All documented hypoglycemia						
Patients with hypoglycemia, n (%)	440 (99.55)	449 (99.56)	325 (98.78)	0.982	0.262	0.251
Number of events	21688	20613	16046			
Non-nocturnal hypoglycemia						
Patients with hypoglycemia, n (%)	421 (95.25)	433 (96.01)	311 (94.53)	0.583	0.641	0.327
Number of events	15293	14198	11645			
Nocturnal hypoglycemia						
Patients with hypoglycemia, n (%)	328 (74.21)	344 (76.27)	251 (76.29)	0.475	0.514	0.999
Number of events	3091	3048	1999			
BG <54 mg/dL, (3.0 mmol/L)						
Documented symptomatic hypoglycemia						
Patients with hypoglycemia, n (%)	290 (65.61)	298 (66.08)	229 (69.60)	0.884	0.245	0.302
Number of events	1601	1508	1224			
All documented hypoglycemia						
Patients with hypoglycemia, n (%)	400 (90.50)	398 (88.25)	298 (90.58)	0.280	0.982	0.311
Number of events	2942	2799	2269			
Non-nocturnal hypoglycemia						
Patients with hypoglycemia, n (%)	329 (74.43)	339 (75.17)	257 (78.12)	0.801	0.241	0.344
Number of events	1937	1826	1563			
Nocturnal hypoglycemia						
Patients with hypoglycemia, n (%)	145 (32.81)	142 (31.49)	100 (30.40)	0.673	0.481	0.749
Number of events	380	279	200			

Abbreviations: BG = blood glucose; CI = confidence interval; LSM = least squares mean; N = number of subjects; SE = standard error.

[a] Logistic regression model for post-baseline comparisons between treatment and control groups: Incidence = Treatment.

[b] LY900014 vs Humalog.

[c] LY900014+20 vs Humalog.

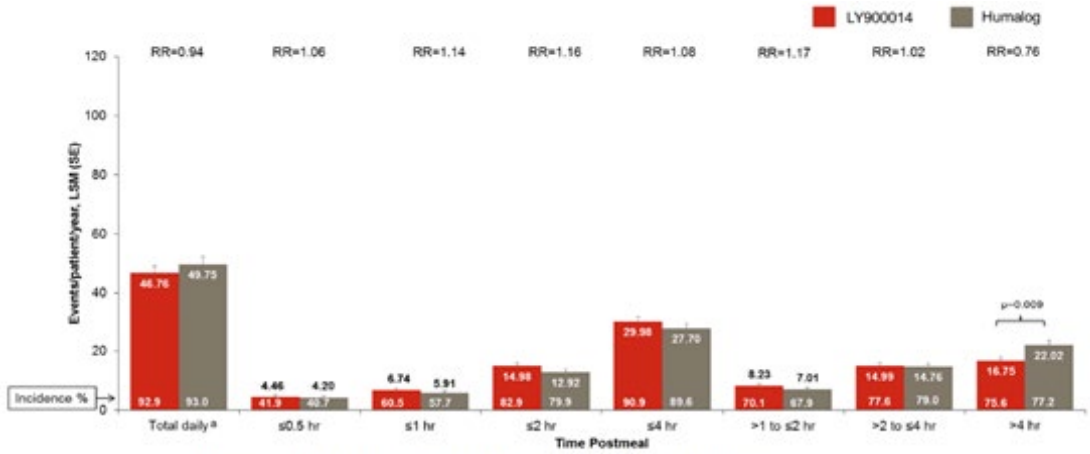
[d] LY900014+20 vs LY900014.

Long-term safety data (ITRM 52-week maintenance)

From baseline to Week 52, the overall incidence and rate of severe hypoglycaemia were similar between the double-blind treatment groups. From baseline to Week 52, there were no significant treatment differences between the double-blind treatment groups in the rate or incidence of nocturnal hypoglycaemia, non-nocturnal hypoglycaemia, all documented hypoglycaemia, and documented symptomatic hypoglycaemia with either glucose threshold (≤3.9 mmol/L [70 mg/dL] or < 3.0 mmol/L [54 mg/dL]). The overall incidence of hypoglycaemic events decreased in the latter part of the study, as an obvious consequence of slight increase in overall glycaemia (HbA1c) from Week 26 to Week 52 in both study arms (Figure 55).

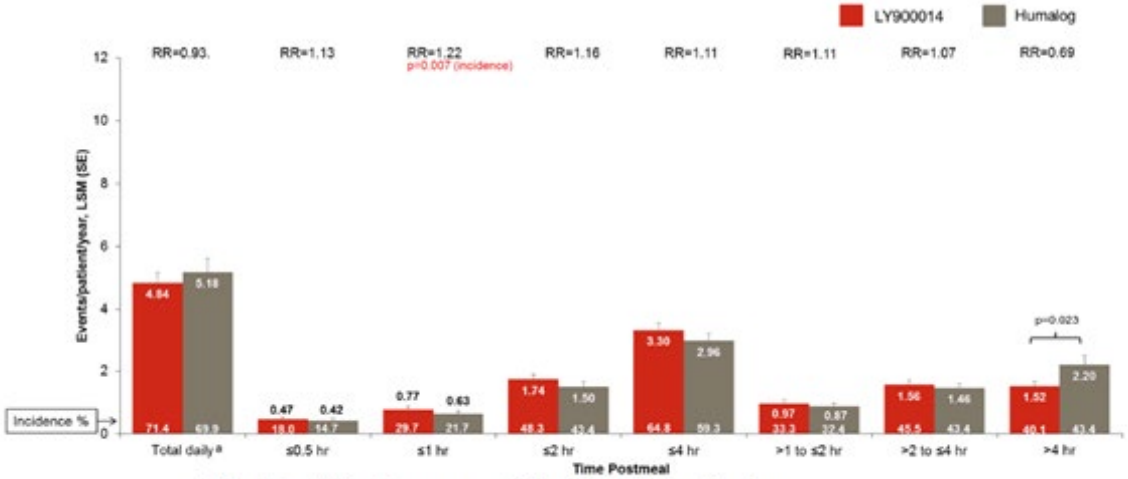
The rate and incidence of postprandial hypoglycaemia was different for the two products. At >4 hours post-meal at both blood glucose (BG) thresholds, the rate of documented symptomatic and of documented symptomatic and asymptomatic hypoglycaemia were statistically significantly lower in the LY900014 versus Humalog group. At ≤1 hour post-meal (BG <3.0 mmol/L [54 mg/dL]), the incidence of documented symptomatic hypoglycaemia and of documented symptomatic and asymptomatic hypoglycaemia were statistically significantly higher in the LY900014 versus Humalog group (Figures 56 and 57).

Figure 55. Rate and incidence (%) of documented symptomatic post-meal hypoglycaemia for 0-52 weeks (BG ≤3.9 mmol/L [≤70 mg/dL])



Abbreviations: LSM = least squares mean; RR = relative rate; SE = standard error.
Event rate data are LSM (SE).
a Rate of daily documented symptomatic hypoglycemia.

Figure 56. Rate and incidence (%) of documented symptomatic postmeal hypoglycaemia for 0-52 weeks (BG ≤3.0 mmol/L [≤54 mg/dL])



Abbreviations: LSM = least squares mean; RR = relative rate; SE = standard error.
Event rate data are LSM (SE).
a Rate of daily documented symptomatic hypoglycemia.

Study ITSI (T1D, CSII)

There was one episode of severe hypoglycaemia in both Humalog and LY900014 groups during study ITSI, and one case of potential severe hypoglycaemia in both groups, too.

The rate and incidence of documented symptomatic hypoglycaemia, all document hypoglycaemia, and non-nocturnal hypoglycaemia rate were higher in the LY900014 group compared to the Humalog group

whether using the BG <3.9 mmol/L threshold or BG <3.0 mmol/L threshold (see Table 29, data given for the last 2 weeks of the 6-week period). This trend was also seen in the incidence of hypoglycaemic events and with BG <3.0 mmol/L. During 0-6 weeks, the documented symptomatic hypoglycaemia rate was higher in the LY900014 group compared to the Humalog group with BG <3.0 mmol/L in ITSI T1D patients (aggregate rate/year 5.81 vs 3.25 respectively; data not shown in Table 29).

Additionally, the incidence of nocturnal hypoglycaemia <3.0mmol/L in the LY900014 group was higher (5 vs. 2 events). When using the BG<3.9 mmol/L threshold, the rate (12.54 vs. 13.92 per year) and incidence (27.7 % vs. 31.9 %) of nocturnal hypoglycaemic events were in the same order of magnitude in the LY900014 group compared with Humalog group (table 30).

Table 29. Hypoglycaemia rate (adjusted for 1 year) and incidence of hypoglycaemia weeks 4 to 6 in each 6-week randomized treatment period, ITSI safety population

		Rate				Incidence		
Category/Subcategory of Hypoglycemia Treatment	N	Mean (SD)	Median	Aggregate Rate/ Year	p-value[a]	n (%)	Episodes	p-value[b]
BG ≤70 mg/dL (3.9 mmol/L)								
Documented symptomatic hypoglycemia								
Humalog	47	45.94 (65.25)	26.09	46.21	0.082	27 (57.4)	83	0.136
LY900014	47	63.61 (94.37)	33.20	60.51		33 (70.2)	111	
All documented hypoglycemia								
Humalog	47	56.91 (66.34)	48.70	56.24	0.031	32 (68.1)	101	0.052
LY900014	47	80.93 (100.89)	48.70	76.32		39 (83.0)	140	
Non-nocturnal hypoglycemia								
Humalog	47	42.99 (57.66)	24.35	42.32	0.014	29 (61.7)	76	0.069
LY900014	47	66.85 (82.24)	48.70	63.78		36 (76.6)	117	
Nocturnal hypoglycemia								
Humalog	47	13.92 (23.36)	0.00	13.92	0.958	15 (31.9)	25	0.728
LY900014	47	14.08 (33.03)	0.00	12.54		13 (27.7)	23	
BG <54 mg/dL (3.0 mmol/L)								
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.

Post-meal hypoglycaemia (T1D)

The rate and incidence of documented symptomatic and asymptomatic post-meal hypoglycaemia (with BG<3.0 mmol/L and <3.9 mmol/L) was smaller in the LY900014 group (premeal administration) compared to Humalog group at >4 hours in T1D patients (Tables 3.3.8.4 and 3.3.8.5).

On the other hand, the incidence and rate of documented symptomatic hypoglycaemia was overall slightly higher at most time points during the first 4 hours after start of the meal in the LY900014 group than in the Humalog group (Tables 3.3.8.4 and 3.3.8.5).

The postprandial administration of LY900014 (LY900014+20) caused slightly more post-meal hypoglycaemia than premeal administration of LY900014. Overall, the differences in rates of hypoglycaemic events between the three groups were small.

Table 30. Documented symptomatic post-meal hypoglycaemia from randomisation to week 26, study ITRM

Category/Subcategory of Hypoglycemia	Rate Per Year LSM (SE)	Relative Rate A: LY900014/Humalog (95% CI), p-value[a] B: LY900014+20/Humalog (95% CI), p-value[a] C: LY900014+20/LY900014 (95% CI), p-value[a]
BG ≤70 mg/dL, (3.9 mmol/L)		
Documented symptomatic hypoglycemia		
≤0.5 hours after start of meal		
Humalog (N=442)	5.19 (0.75)	A: 1.06 (0.71, 1.57), p=0.788
LY900014 (N=451)	5.48 (0.78)	B: 1.43 (0.93, 2.21), p=0.107
LY900014+20 (N=329)	7.42 (1.24)	C: 1.35 (0.88, 2.08), p=0.167
Documented symptomatic hypoglycemia		
≤1 hour after start of meal		
Humalog (N=442)	7.57 (0.84)	A: 1.11 (0.82, 1.50), p=0.486
LY900014 (N=451)	8.42 (0.90)	B: 1.24 (0.87, 1.76), p=0.232
LY900014+20 (N=329)	9.37 (1.31)	C: 1.11 (0.79, 1.57), p=0.545
Documented symptomatic hypoglycemia		
≤2 hours after start of meal		
Humalog (N=442)	16.67 (1.25)	A: 1.14 (0.93, 1.40), p=0.192
LY900014 (N=451)	19.07 (1.35)	B: 1.06 (0.85, 1.32), p=0.624
LY900014+20 (N=329)	17.62 (1.50)	C: 0.92 (0.74, 1.15), p=0.476
Documented symptomatic hypoglycemia		
≤4 hours after start of meal		
Humalog (N=442)	34.17 (1.90)	A: 1.09 (0.94, 1.27), p=0.265
LY900014 (N=451)	37.26 (2.02)	B: 1.11 (0.95, 1.30), p=0.200
LY900014+20 (N=329)	37.93 (2.25)	C: 1.02 (0.87, 1.19), p=0.825
Documented symptomatic hypoglycemia		
>1 to ≤2 hours after start of meal		
Humalog (N=442)	9.10 (0.79)	A: 1.17 (0.92, 1.49), p=0.198
LY900014 (N=451)	10.64 (0.91)	B: 0.91 (0.71, 1.16), p=0.431
LY900014+20 (N=329)	8.25 (0.72)	C: 0.78 (0.61, 0.99), p=0.038
Documented symptomatic hypoglycemia		
>2 to ≤4 hours after start of meal		
Humalog (N=442)	17.49 (1.10)	A: 1.04 (0.87, 1.24), p=0.670
LY900014 (N=451)	18.19 (1.20)	B: 1.16 (0.96, 1.41), p=0.128
LY900014+20 (N=329)	20.30 (1.52)	C: 1.12 (0.92, 1.36), p=0.270
Documented symptomatic hypoglycemia		
>4 hours after start of meal		
Humalog (N=442)	26.00 (1.94)	A: 0.76 (0.63, 0.93), p=0.009
LY900014 (N=451)	19.89 (1.38)	B: 0.85 (0.69, 1.05), p=0.133
LY900014+20 (N=329)	22.11 (1.73)	C: 1.11 (0.91, 1.36), p=0.311

Abbreviations: BG = blood glucose; CI = confidence interval; LSM = least squares mean; N = number of subjects; SE = standard error.

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

Table 31. Documented symptomatic post-meal hypoglycaemia rate (adjusted for 1 year) and incidence by post-meal time interval weeks 4 to 6 in each 6-week randomized treatment period prior to discontinuation of study drug, ITSI safety population

Category of Hypoglycemia		Rate				Incidence		
Time Point Treatment	N	Mean (SD)	Median	Aggregate Rate/Year	p-value[a]	n (%)	Episodes	p-value[b]
Documented symptomatic hypoglycemia, BG ≤70 mg/dL (3.9 mmol/L)								
≤0.5 hours after start of meal								
Humalog	47	4.48 (13.86)	0.00	5.01	1.00	5 (10.6)	9	0.999
LY900014	47	5.56 (20.16)	0.00	6.54		5 (10.6)	12	
≤1 hour after start of meal								
Humalog	47	9.19 (20.86)	0.00	9.47	0.578	9 (19.1)	17	0.488
LY900014	47	8.32 (21.00)	0.00	9.27		10 (21.3)	17	
≤2 hours after start of meal								
Humalog	47	14.61 (30.47)	0.00	15.03	0.205	14 (29.8)	27	0.047
LY900014	47	18.45 (27.15)	0.00	19.08		21 (44.7)	35	
≤4 hours after start of meal								
Humalog	47	26.04 (43.92)	0.00	26.73	0.127	20 (42.6)	48	0.199
LY900014	47	35.08 (51.18)	20.29	34.34		25 (53.2)	63	
>1 to ≤2 hours after start of meal								
Humalog	47	5.41 (15.03)	0.00	5.57	0.049	7 (14.9)	10	0.034
LY900014	47	10.13 (17.49)	0.00	9.81		14 (29.8)	18	
>2 to ≤4 hours after start of meal								
Humalog	47	11.43 (21.42)	0.00	11.69	0.246	13 (27.7)	21	0.467
LY900014	47	16.63 (35.32)	0.00	15.26		11 (23.4)	28	
>4 hours after start of meal								
Humalog	47	19.90 (36.81)	0.00	19.49	0.569	17 (36.2)	35	0.451
LY900014	47	28.53 (54.34)	0.00	26.17		20 (42.6)	48	

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

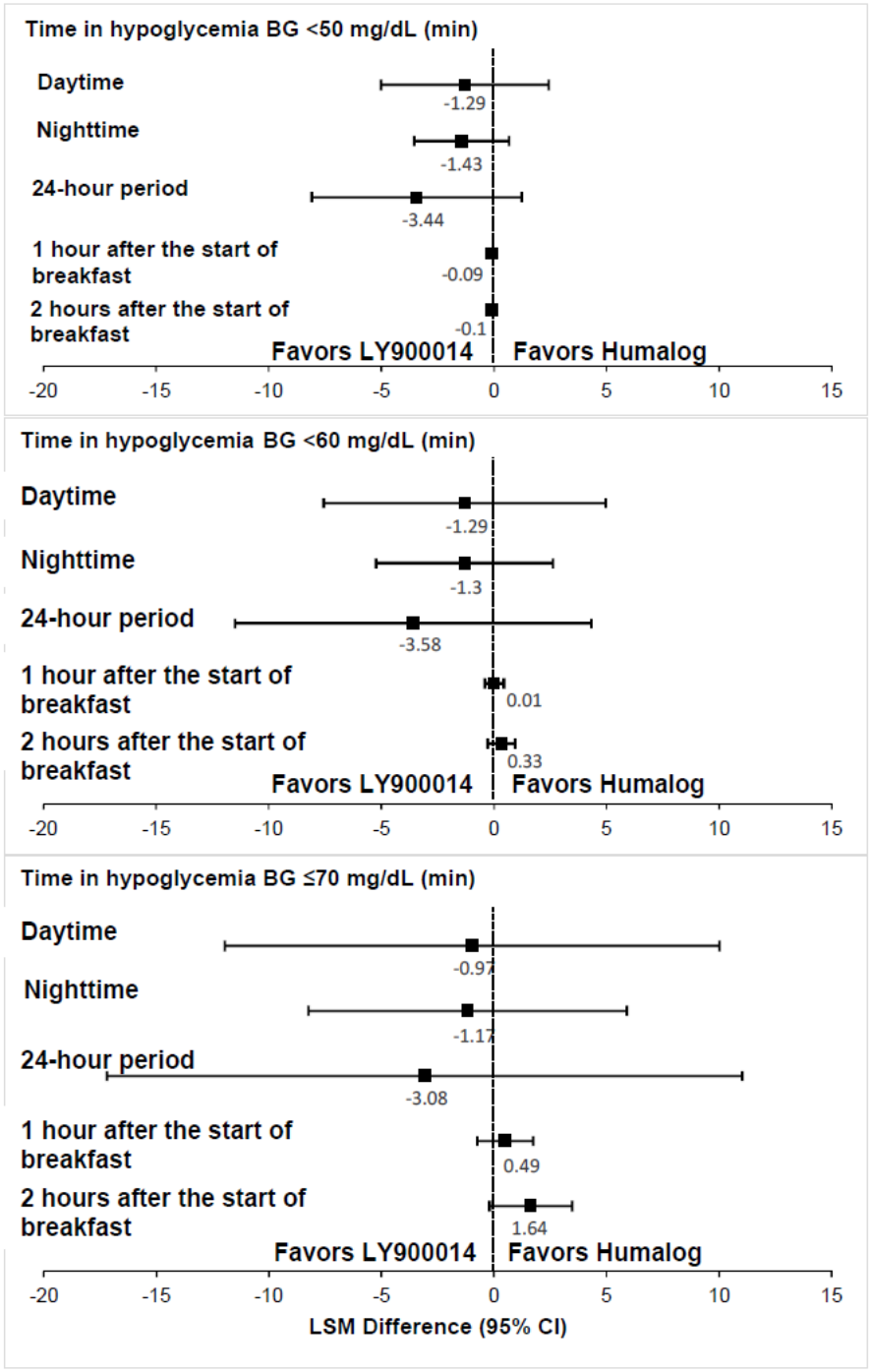
Time with glucose in hypoglycaemic ranges (T1D)

Continuous glucose monitoring was used in the ITSI study (T1D, CSII) and in the ITRM CGM substudy (T1D).

In ITSI, duration of time (percentage and minutes) in hypoglycaemia was analysed for daytime, night-time, and 24-hour periods, by infusion set wear day for each 6-week treatment period. The results are presented in Figure 3.3.8.1 (Weeks 4 to 6 of the 6-week treatment period).

- On Day 1 of infusion set wear, in the LY900014 group, shorter mean duration of time with glucose <2.8 mmol/L, <3.3 mmol/L and ≤3.9 mmol/L during the 24-hour period was observed compared to Humalog:
    - <2.8 mmol/L (LSM): LY900014, 9.55 minutes; Humalog, 17.97 minutes
    - <3.3 mmol/L (LSM): LY900014, 28.74 minutes; Humalog, 42.87 minutes
    - ≤3.9 mmol/L (LSM): LY900014, 69.18 minutes; Humalog, 95.35 minutes
- On Days 2 and 3 of infusion set wear, more time in hypoglycaemia with glucose ≤3.9 mmol/L was observed for LY900014-treated patients vs. Humalog.

Figure 57. Time spent in hypoglycaemia (ITSI study, weeks 4 to 6 of 6-week treatment period)

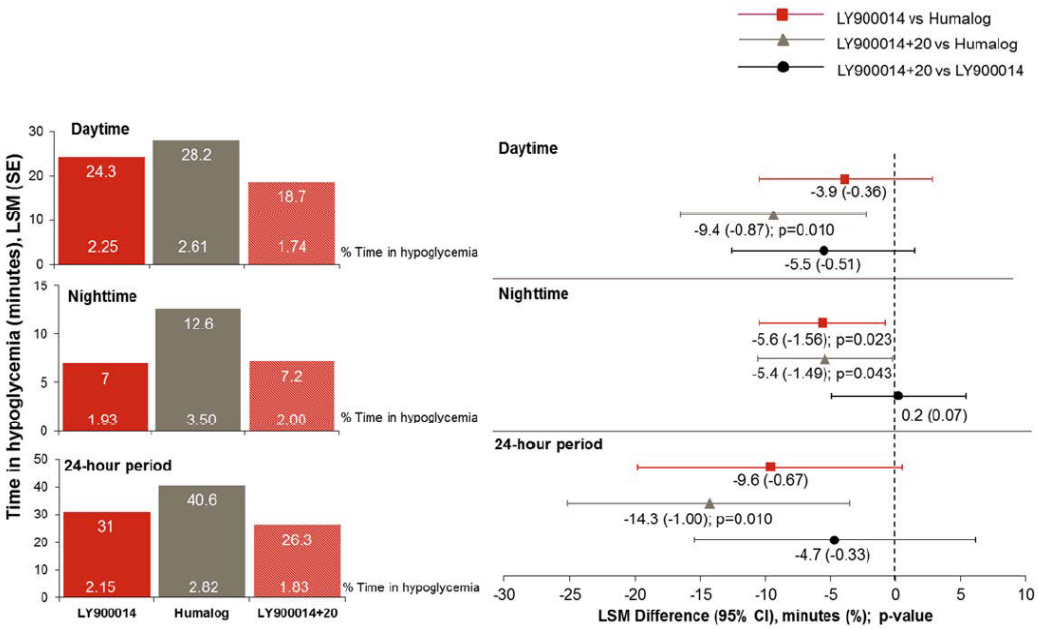


Abbreviations: CI = confidence interval; LSM = least squares mean.
Source: /lillyce/prd/ly900014/i8b_mc_itsi/final/output/shared/tfl/smcgt04.rtf.

BG conversion: 50 mg/dL = 2.8 mmol/L; 60 mg/dL = 3.3 mmol/L, 70 mg/dL = 3.9 mmol/L.

In the ITRM CGM substudy, the results on the analyses of time in hypoglycaemia similarly demonstrated that LY900014 was associated with somewhat less time in hypoglycaemia in comparison with Humalog. (Figure 58).

Figure 58. Time spent in hypoglycaemia (BG <2.8 mmol/L) at Week 26. ITRM CGM substudy



Abbreviations: CI = confidence interval; LSM = least squares mean; SE = standard error.

The CGM-based follow-up indicates that there would be slightly less hypoglycaemia in T1D patients when using LY900014 instead of Humalog. In the ITRM study overall, there were no statistical differences between LY900014 and Humalog in hypoglycaemia incidence overall. However, in the ITSI study, there were non-significantly more hypoglycaemias in the LY900014 group within 4 hours after meal as measured by SMBG. The SMBG measurements and CGM results are, however, not comparable, as the latter method gives data from more time points, including asymptomatic hypoglycaemia; whereas the SMBG results are not only routine measurements, but also contain measurements performed due to hypoglycaemic symptoms.

T2D/study ITRN

During the 26 weeks in ITRN (T2D), the incidence of **severe hypoglycaemia** was 7 episodes/337 subjects in the Humalog groups and 4 episodes/336 subjects in the LY900014 group; and the aggregate rate/100 years was 4.19 vs. 2.44 in the Humalog and LY90014 groups, respectively.

In ITRN T2D patients, higher **documented symptomatic hypoglycaemia** rate (with BG <3.0 mmol/L) was observed in the LY900014 group compared to the Humalog group. Also, higher rate and incidence of **non-nocturnal hypoglycaemia** (with BG ≤3.9 mmol/L) was observed in the LY900014 group compared to the Humalog group (see Table 32).

Table 32. Hypoglycaemia rate (adjusted for 1 year) and incidence from randomization to week 26 prior to discontinuation of study drug (ITRN safety population)

Category/Subcategory of Hypoglycemia Treatment	N	Rate LSM (SE)	Rate p-value[a]	Incidence n (%)	Incidence Episodes	Incidence p-value[b]
BG ≤70 mg/dL (3.9 mmol/L)						
Documented symptomatic hypoglycemia						
Humalog	337	13.23 (1.29)	0.120	207 (61.42)	2220	0.069
LY900014	336	16.21 (1.40)		229 (68.15)	2707	
All documented hypoglycemia						
Humalog	337	32.92 (1.88)	0.321	317 (94.07)	5509	0.506
LY900014	336	35.68 (2.05)		320 (95.24)	5923	
Non-nocturnal hypoglycemia						
Humalog	337	19.86 (1.44)	0.042	258 (76.56)	3312	0.038
LY900014	336	24.31 (1.64)		279 (83.04)	4051	
Nocturnal hypoglycemia						
Humalog	337	4.46 (0.53)	0.592	161 (47.77)	748	0.420
LY900014	336	4.06 (0.51)		171 (50.89)	676	
BG <54 mg/dL (3.0 mmol/L)						
Documented symptomatic hypoglycemia						
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 hypoglycemia						
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 hypoglycemia						
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 hypoglycemia						
Humalog	337	0.53 (0.09)	0.276	55 (16.32)	89	0.410
LY900014	336	0.68 (0.11)		63 (18.75	113	

Hypoglycemia Rate (Adjusted for 1 Year) and Incidence for Each Category and Subcategory of Hypoglycaemia From Randomization to Week 26 Prior to Discontinuation of Study Drug
Safety Population, Study ITRN

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.

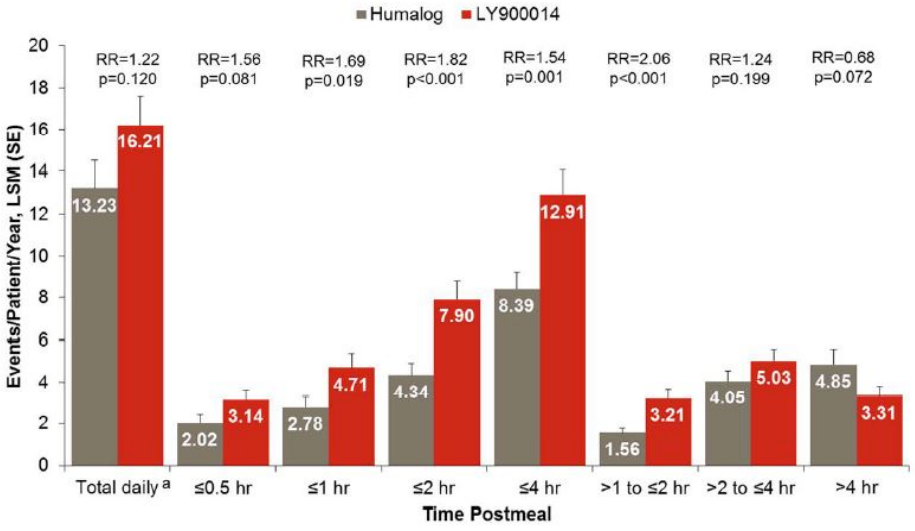
[a] Negative binomial model for postbaseline comparisons between treatment and control groups: Number of episodes = Treatment with log (exposure in days/365.25) as an offset variable.

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

Post-meal hypoglycaemia (T2D)

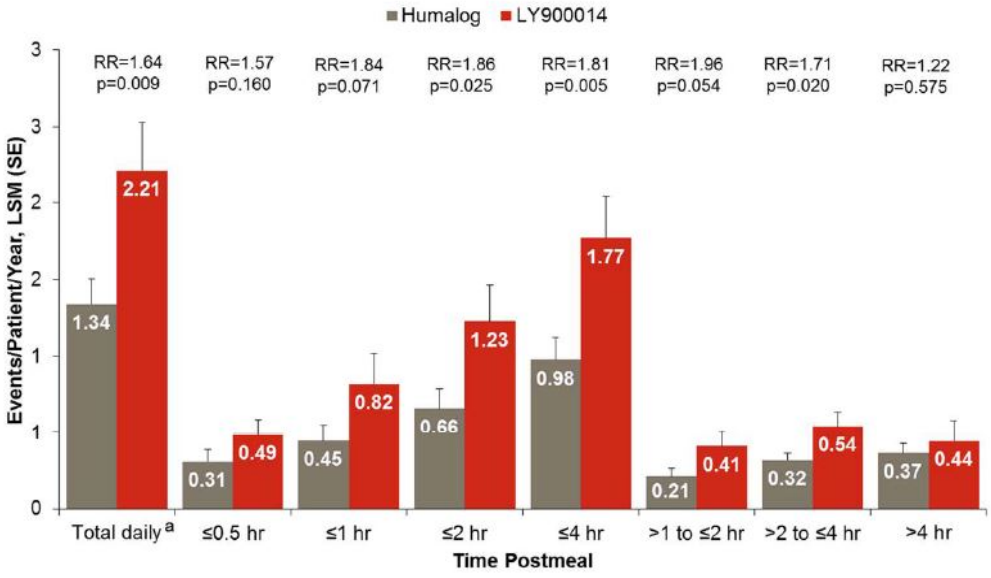
In T2D patients the rate of both symptomatic as well as symptomatic and asymptomatic post-meal hypoglycaemia was higher with BG <3.9 mmol/L in the LY900014 group compared to the Humalog group at all hourly time intervals up to 4 hours post-meal. Only after 4 hours from meal, rates of hypoglycaemic events between Humalog and LY900014 were overall similar. When combining documented symptomatic and asymptomatic post-meal hypoglycaemic events, the rate was higher in the Humalog group after 4 hours. (See Figures 3.3.8.3–3.3.8.6.)

Figure 59. Rate of daily and documented symptomatic post-meal hypoglycaemia (BG 3.9 mmol/L), ITRN



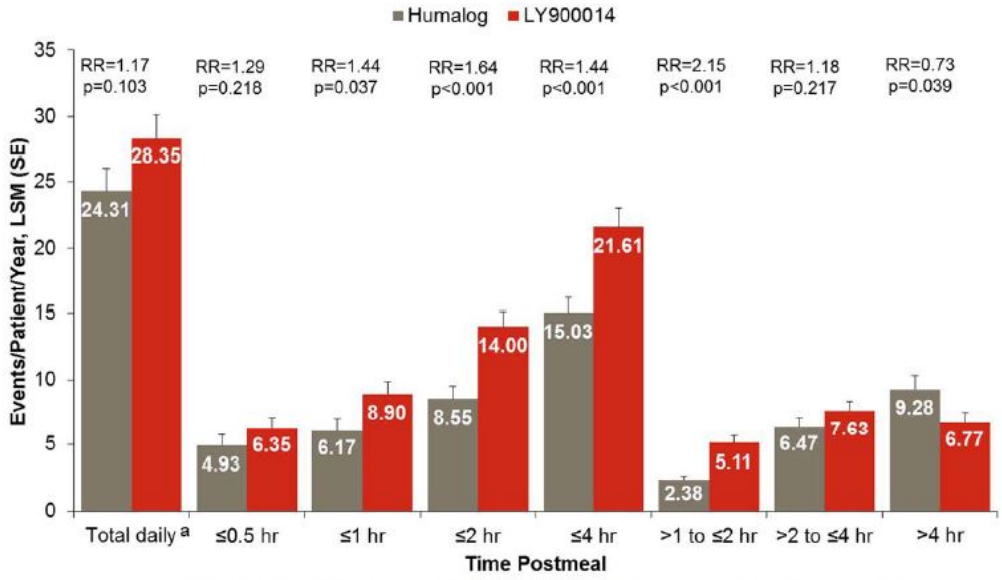
Abbreviations: BG = blood glucose; LSM = least squares mean; RR = relative rate; SE=standard error.
[a] Rate of daily documented symptomatic hypoglycemia.

Figure 60. Rate of daily and documented symptomatic post-meal hypoglycaemia (BG 3.0 mmol/L), ITRN



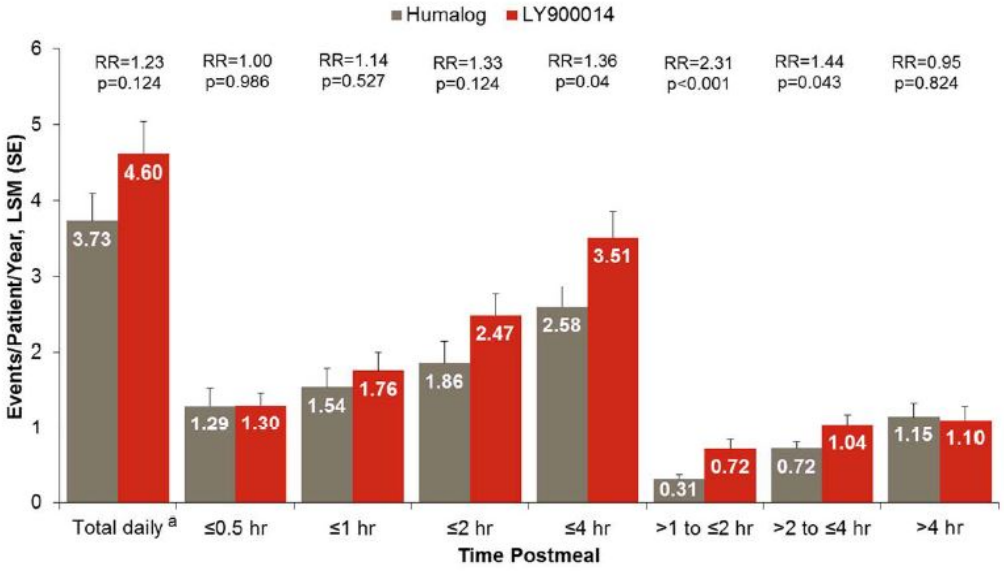
Abbreviations: BG = blood glucose; LSM = least squares mean; RR = relative rate; SE = standard error.
[a] Rate of daily documented symptomatic hypoglycemia.

Figure 61. Rate of daily and documented symptomatic and asymptomatic post-meal hypoglycaemia (BG 3.9 mmol/L), ITRN



Abbreviations: BG = blood glucose; LSM = least squares mean; RR = relative rate; SE = standard error.
[a] Rate of daily documented asymptomatic and symptomatic hypoglycemia.

Figure 62. Rate of daily and documented symptomatic and asymptomatic post-meal hypoglycaemia (BG 3.0 mmol/L)



Abbreviations: BG = blood glucose; LSM = least squares mean; RR = relative rate; SE=standard error.
[a] Rate of daily documented asymptomatic and symptomatic hypoglycemia.

Laboratory findings

No concern arose about elevated liver enzymes or bilirubin. No between-group differences were seen in other laboratory parameters either. These conclusions are based on ITRM and ITRN studies only, as in ITSI no post-baseline measurements were taken.

No concern arose about laboratory findings in clinical pharmacology studies.

Safety in special populations

Differences were seen in BMI sub-groups in relation to nasopharyngitis, but the results were contrary to the treatment groups in different high BMI categories, which leads to the conclusion that the clinical importance might be scarce.

The Applicant presented upon request hypoglycaemia events from studies ITRM, ITRN and ITSI (separately) in age categories <65, ≥65 years and filled out a table on adverse reactions for each age group. Severe hypoglycaemic events occurred in very few subjects above the age of 65, and no obvious difference was seen between study arms in severe hypoglycaemia. The rates of hypoglycaemia were not statistically different in subjects below 65 years of age and ≥65 years of age. However, as the numbers of subjects ≥65 years of age were relatively low, the comparison lacks statistical power. Numerically, the rate of all documented hypoglycaemic events and for documented symptomatic hypoglycaemic events (events/patient/year) decreased by age in both Humalog and LY90014 groups, whether using the threshold of <3.0 mmol/L or <3.9 mmol/L. The rate of hypoglycaemic events was overall similar in Humalog and LY900014+20 (post-meal administration) groups in the ITRM study; and slightly lower in the prandial LY900014 group.

The obvious explanation for lower rates of hypoglycaemia in subjects above 65 years is that the glycaemic control was not as strict in the elderly subjects as in younger patients (see assessment of Question 85), which is also in line with treatment guidelines.

The incidence of TEAE was comparable between Humalog and LY900014 in all age groups. There are no consistent differences in occurrence of any AE class, although there were some differences that can be interpreted as chance differences among a large number of comparisons (data not included for brevity).

Four pregnancies were reasons for study discontinuation in Study ITRM in women receiving LY900014. Three pregnancies ended in spontaneous abortion and one was an empty sac. All cases were considered to be not related to study drug by investigator.

Immunological events

In the population PK analysis, baseline ADA status was a significant covariate on insulin lispro clearance. Of all patients in the Phase 3 and clinical pharmacology studies, 42.5% (918 of 2160) of were ADA positive at baseline. There was a small decrease in clearance (16.5%) in ADA-positive vs. ADA-negative subjects. Regardless of this, the baseline ADA status did not impact either the PK and glucodynamic faster time-action profile or safety of LY900014 compared to Humalog.

Both MDI studies (ITRM in T1D and ITRN in T2D) provide immunogenicity data from a 26-week controlled, parallel-group period, including evaluation of potential effect of immunogenicity on efficacy endpoints, insulin dose, and safety. The T1DM study ITRM had additionally a 6-month safety extension period that was ongoing at the time of the dossier cut-off date for data inclusion. The Week 52 data up to end of safety period of ITRM were submitted in the D120 response and the final immunogenicity data from the ADA follow-up period with the D150 response. ADA were also measured in the ITSI study comparing in a cross-over setting LY900014 and Humalog when used as CSII.

ITRM (T1D): ADA and TEADA

In Study ITRM (T1D), similar proportions of patients in each treatment group had detectable ADA at baseline, i.e. at the beginning of double-blind period: LY900014, 47.8%; LY900014+20, 49.8%; Humalog, 44.2%. Hence, there were more ADA-positive subjects in the LY900014 arms already before exposure to LY900014, since all subjects had received Humalog during the lead-in period. Overall, from Week 0 to Week 26, there were similar proportions of patients in each treatment group with

treatment-emergent anti-insulin lispro antibodies (TEADA) (table 33). At end of long-term maintenance period i.e. Week 52, the proportions of patients with TEADA had decreased and was significantly different in the Humalog and LY900014 groups: 11.8 % and 15.6 %, respectively. The LY900014+20 group was not continued after Week 26.

Table 33. Immunogenicity results in T1D (ITRN) and T2D (ITRM)

			Baseline		Assessment Period, Weeks 0 to 26			
			ADA Present Patients		TEADA+ Patients (at any visit)			
Study	Treatment	Patients with Evaluable ADA	Total[a] n (%)	Cross-reactive ADA[b] n (%)	Total[a] n (%)	Treatment Induced ADA[a] n (%)	Treatment Boosted ADA[a] n (%)	Cross-reactive ADA[c] n (%)
ITRM	LY900014	777	378 (48.6)	345 (91.3)	255 (32.8)	150 (19.3)	105 (13.5)	191 (74.9)
	Humalog	441	195 (44.2)	173 (88.7)	141 (32.0)	84 (19.0)	57 (12.9)	108 (76.6)
	Total	1218	573 (47.0)	518 (90.4)	396 (32.5)	234 (19.2)	162 (13.3)	299 (75.5)
ITRN	LY900014	335	116 (34.6)	94 (81.0)	103 (30.7)	72 (21.5)	31 (9.3)	70 (68.0)
	Humalog	337	116 (34.4)	101 (87.1)	80 (23.7)	61 (18.1)	19 (5.6)	51 (63.8)
	Total	672	232 (34.5)	195 (84.1)	183 (27.2)*	133 (19.8)	50 (7.4)	121 (66.1)

Abbreviations: ADA = antidrug antibodies; n = number of patients; TEADA = treatment-emergent antidrug antibodies.

[a] The percentage was calculated using patients with evaluable ADA as the denominator.

[b] The percentage was calculated using the total number of patients who were ADA present as the denominator.

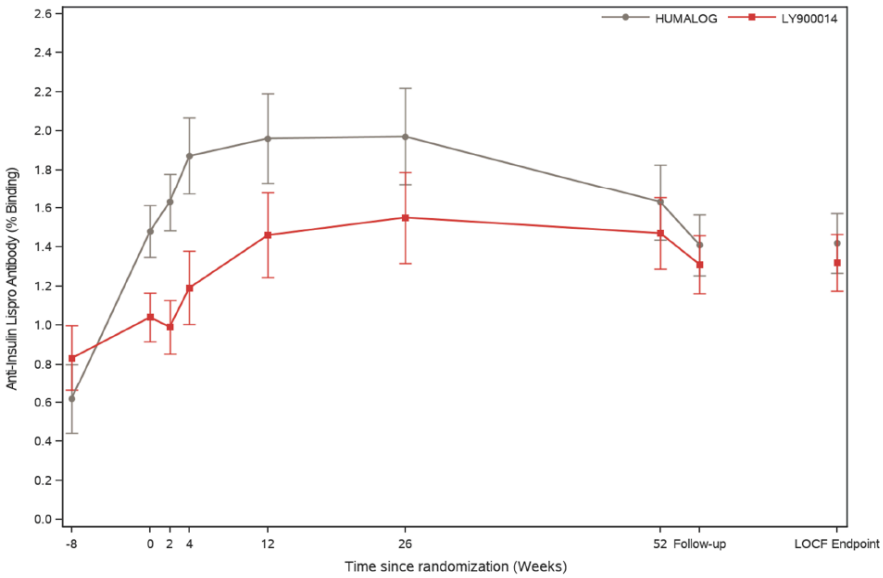
[c] The percentage was calculated using the total number of patients who were TEADA+ as the denominator.

* P-value < 0.05; for treatment comparison from Fisher exact test, Humalog vs LY900014.

Patients with TEADA who had not returned to baseline were further entered in the ADA follow-up period, where they were followed at approximately 3-month intervals for a maximum of 6 months or until insulin lispro antibodies of the subject returned to baseline range, whichever occurred sooner. Of all randomized patients in ITRM, 147 (12%) met the criteria to enter the ADA follow-up period: 45, 55, and 47 in the Humalog, LY900014, and LY900014 postmeal groups, respectively. Of these, 131 (89.1%) completed the period.

Throughout the lead-in, treatment and safety follow-up periods of ITRM, the mean anti-insulin lispro levels (percent binding) were low. In patients with TEADA, the ADA percent binding was slightly higher in the Humalog group than in the LY900014 group (Figure 63). This difference in ADA levels between study arms was no more seen during the ADA follow-up period. The number of patients with TEADA decreased during the period: from 147 patients at visit 801 to 75 patients at visit 802, and 46 patients at visit 803.

Figure 63. ADA (mean % binding) from study entry to safety follow-up for patients with TEADA, ITRM



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: /lillyce/prd/ly900014/i8b mc itrm/csr2/output/shared/grada04.rtf.

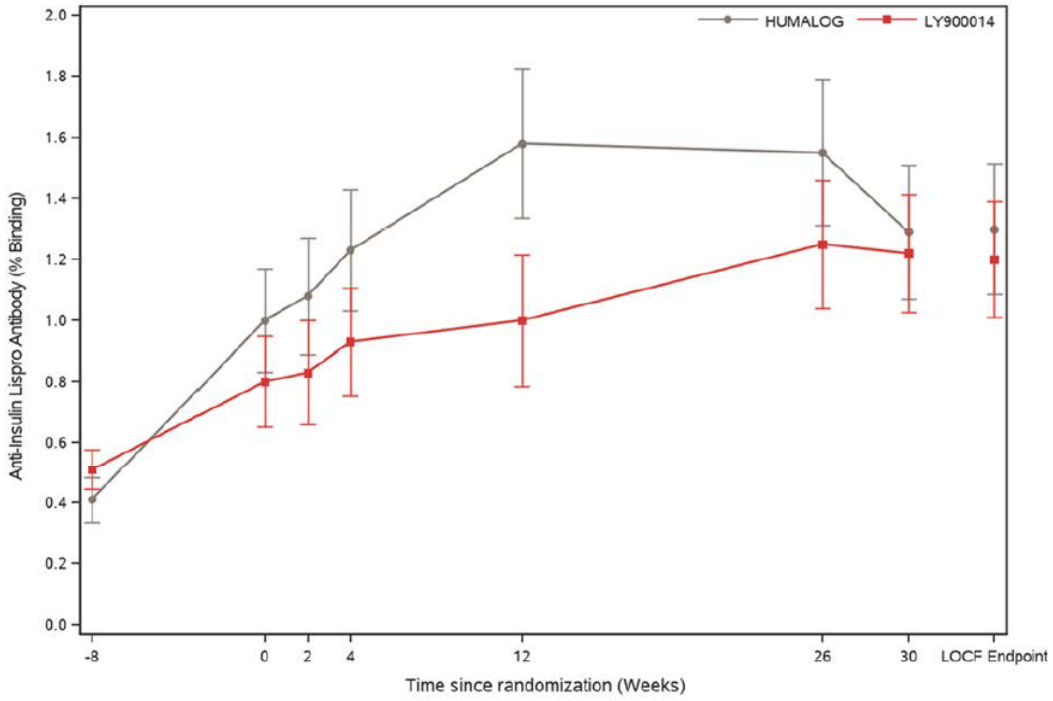
ITRN (T2D): ADA and TEADA

In Study ITRN (T2D), similar proportions of patients in each treatment group had detectable ADA at the beginning of the double-blind treatment period (LY900014, 34.6%; Humalog, 34.4%).

From week 0 to 26, more patients in the LY900014 group (30.7%) had TEADA compared with the Humalog group (23.7%). However, the numbers of subjects with TEADA decreased during the safety follow-up, and the difference was no more significant at the safety follow-up visit at Week 30 (proportion of TEADA-positive subjects 12.3% and 15.7 % in the in the Humalog and LY000014 groups, respectively).

Over the course of Study INTR (T2D), most patients who developed TEADA had low % binding values and were cross reactive to native insulin. However, similar to T1D patients in ITRM, there was a trend for higher ADA percent binding levels in TEADA-positive subjects in the Humalog group than in the LY900014 group (figure 64).

Figure 64. ADA (mean % binding) from lead-in to safety follow-up period for patients with TEADA, ITRN



Note: Data are LSM (SE).
Abbreviation: LOCF = last observation carried forward; LSM = least squares mean; SE = standard error; TEADA = treatment emergent anti-insulin lispro antibody.
Source: /lillyce/prd/ly900014/i8b_mc_itrn/csr1/output/shared/grada01.pdf.

A total of 89 patients (13% of randomized patients in study ITRN; 39 in the Humalog and 50 in the LY900014 group) met the criteria for the antibody follow-up period, of whom 82 completed the antibody follow-up period. During the ADA follow-up, the number of patients with TEADA decreased from 89 patients at visit 801 to 28 patients at visit 803. Also, the percent binding levels of TEADA in these patients decreased already during the safety follow-up period (figure 3.3.8.10) and were comparable during the ADA follow-up period (data not shown). ADA levels did not correlate with HbA1c results or insulin doses in T2D subjects.

In ITSI, 26 patients (53.1%) had TEADA, with 12 (24.5%) having treatment-induced ADA, and 14 (28.6%) having treatment-boosted ADA. 24 (92.31%) of the 26 patients with TEADA were positive for antibodies cross-reactive with native insulin. 9 (34.62%) of the 26 patients with TEADA had antibody levels (% binding) return to baseline at the last postbaseline visit. As all patients in ITSI were exposed to both LY90014 and Humalog, no comparison between treatments was performed.

Impact of TEADA on clinical effects:

Glycaemic control

Throughout studies ITRM and ITRN, there were no treatment-by-TEADA interactions in overall glycaemic control (as measured by HbA1c) or basal, prandial, or total insulin doses.

However, T1D patients with positive TEADA status treated with LY900014 had a significantly lower bolus:total insulin ratio than patients treated with Humalog (p=0.024) in the ITRM study. There was also a significant treatment-by-TEADA interaction for the 1-hour PPG excursion (p=0.039), but not for the 2-hour PPG excursion, during the treatment period of 0 to 26 weeks in the ITRM study. Hence, some but

not all of the benefit on early PPG excursion by using LY900014 vs. Humalog was lost in TEADA-positive T1D subjects without effect on overall glycaemic control.

In ITRN, there was no treatment-by-TEADA interaction on PPG excursions.

No differential treatment effect was seen on overall hypoglycaemia rates in Studies ITRM and ITRN for patients with or without TEADA.

Hypersensitivity reactions

In Study ITRM (T1D), a higher percentage of LY900014-treated patients with TEADA (LY900014, n=6 [3.9%]; LY900014+20, n=5 [4.9%]) reported potential systemic hypersensitivity reactions (narrow MedDRA search terms) compared to patients without TEADA (LY900014, n=6 [2.0%]; LY900014+20, n=4 [1.8%]). On the contrary, in the Humalog group, potential systemic hypersensitivity reactions were more frequent in patients without TEADA (n=8 [2.7%]) than in patients with TEADA (n=0).

In T2D patients in Study ITRN, similar percentages of LY900014- and Humalog-treated patients with TEADA (LY900014, 2 [1.7%]; Humalog, 2 [2.2%]) and without TEADA (LY900014, n=4 [1.8%]; Humalog, n=6 [n=2.4%]) reported potential systemic hypersensitivity reactions (narrow MedDRA search terms). There were too few treatment-emergent systemic hypersensitivity reactions to analyse treatment-by-TEADA interaction.

In both T1D and T2D, treatment-emergent injection site reactions occurred similarly in patients with and without TEADA. The proportions of patients with injection site reaction related events, study arms combined, were as follows:

- ITRM: patients without TEADA (2.2%) and patients with TEADA (1.9%).
- ITRN: patients without TEADA (2.1%) and patients with TEADA (1.3%).

As a conclusion, about half of T1D patients and one third of T2D patients were ADA-positive at baseline of the studies ITRN and ITRM, with high prevalence of cross-reactivity to native insulin. The proportion of subjects with TEADA was similar across study arms in ITRM (T1D). In T2D patients, evolution of TEADA was more frequent in patients administered LY900014 than Humalog during the treatment period of the study. On the other hand, ADA percent binding levels in TEADA-positive subjects were slightly higher in the Humalog arm in both T1D and T2D subjects. However, the difference in ADA levels decreased during the safety follow-up and was no more present during the ADA follow-up period of either ITRM or ITRN.

ADA-positivity did not affect overall efficacy or hypoglycaemic events in either T1D or T2D subjects. TEADA affected slightly antihyperglycaemic effect at 1 hour in T1D, but not in T2D subjects; no effect on overall glycaemia was observed in either T1D or T2D subjects. Local hypersensitivity reactions were not consistently associated with TEADA. Systemic hypersensitivity reactions were scarce. The 10-fold increased frequency of local hypersensitivity reactions at injection site in patients administered LY900014 vs. Humalog is not explained by immunogenicity.

Safety related to drug-drug interactions and other interactions

No structured DDI studies were conducted for LY900014; this approach was agreed by CHMP during SA (EMA/CHMP/SAWP/400498/2016).

In ITRN, the patients were allowed to continue the use of up to 2 OAMs: metformin (70.6% at baseline) and SGLT2 inhibitor (17.7% at baseline) during the lead-in and treatment periods. In ITRM and ITRN

overall, the All LY and Humalog groups were generally balanced with respect to concomitant medications, with 88.3% of patients using ≥1 concomitant medication. The most frequently used concomitant drugs were lipid modifying agents (45.6%), antithrombotic agents (25.1%), and analgesics and antipyretics (23.4%). Statistically significant treatment differences were observed for clopidogrel (All LY, 2.4%; Humalog, 1.4%; p=0.017), thyroid preparations (All LY, 13.7%; Humalog, 17.7%; p=0.006), and levothyroxine (All LY, 4.4%; Humalog, 6.8%; p=0.022).

In ITSI, the most frequently used medications by category were lipid modifying agents (14 patients [28.6%]) and thyroid preparations (10 patients [20.4%]). The most frequently reported medications were levothyroxine sodium (9 patients [18.4%]) and fish oil (5 patients [10.2%]).

Discontinuation due to adverse events

In the Phase 3 MDI studies (integrated safety database), the frequency of patients with at least one AE leading to discontinuation of study drug was low and similar between the All LY (17/1895 [1.5%]) and Humalog (8/779 [1.0%]) treatment groups. Maternal exposure before pregnancy was the most common AE leading to treatment discontinuation in ITRM and ITRN. One patient receiving LY900014 discontinued the study due to a TEAE of injection site oedema.

There were no discontinuations due to an AE during Study ITSI.

In the integrated clinical pharmacology studies, five subjects were discontinued due to AE: two subjects in the LY900014 group (1 nasopharyngitis, 1 moderate hypoglycaemia) and two in the Humalog group (1 moderate hypotension and 1 mild hyperglycaemia), and one prior to receiving study treatment (increased systolic blood pressure). In addition to these 5 events, 1 patient decided to withdraw due to concern about study procedures (perceived risks), and 1 patient was withdrawn due to physician decision: safety risk due to multiple hypoglycaemic events.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The active substance insulin lispro is known for more than 20 years. The present MAA concerns use in adults only. A new excipient, treprostinil, is present in the product.

In total, the Applicant had performed 22 clinical pharmacology studies (in addition to 3 phase 3 studies).

A total of 1165 patients received LY900014 in the three Phase 3 studies a.k.a. ITRM, ITRN and ITSI. Of these patients, 921 received LY900014 as multiple daily injections for at least 180 days, and 33 received LY900014 via pump for at least 42 days. In clinical pharmacology studies, a total of 294 subjects (74 healthy subjects and 220 patients with T1D or T2D) received at least 1 dose of study drug (either LY900014 or Humalog).

For safety analyses, the Applicant pooled safety results from the Phase 3 MDI studies ITRM and ITRN (except for immunogenicity and hypoglycaemic events) up to the 26-week follow-up. Data from LY900014 and LY900014+20 are pooled as 1 treatment group (All LY) for comparison with Humalog. Safety results from the long-term maintenance period of ITRM (T1D) were submitted in by the Applicant with the D121 responses.

Depending on the nature of the safety data, different statistical methods have been applied in the analysis of it. The methods as such are acceptable, however, the statistical analysis of the safety data is not controlled for type I error rate, nor the studies are powered for demonstration of differences, thus the low p-values can be only considered as indicative of potential treatment difference, and similarly higher p-value may indicate no difference or lack of power to detect difference.

Common AE

In ITRM and ITRN, no differences in AEs in general were seen between the study groups in pooled data, but in ITSI, the TEAEs (all and related to study drug) were more than twice as common in the LY900014 arm than in the Humalog arm. Also in the clinical pharmacology studies, TEAEs were more common in healthy subjects receiving LY900014 than in healthy subjects receiving Humalog, and this was highlighted in TEAEs related to study treatment. The difference in TEAE frequency in ITSI and clinical pharmacology studies was driven by a higher incidence of injection and infusion site reactions in subjects administered LY900014. In all patients, the most common TEAEs related to study drug were hypoglycaemia, headache and injection site reaction.

Serious adverse events and deaths

In the Phase 3 MDI studies (integrated safety data base), the percentage of patients reporting at least 1 SAE was similar in the All LY and Humalog groups (7.7% and 8.5%, respectively). The most frequently (≥3 All LY patients) reported SAEs were hypoglycaemia, pneumonia, cellulitis, and chronic obstructive pulmonary disease. No relevant treatment differences and no clinically important differences were observed between patients in the All LY and Humalog groups with respect to SAEs.

In Study ITSI, the overall incidence of SAEs was low. Two patients (LY900014, 1 [2.0%]; Humalog, 1 [2.1%]) reported SAEs, both were events of hypoglycaemia.

There were ten death events in studies ITRM (T1D) and ITRN (T2D), none of which were considered by the investigator to be related to study drug. No deaths occurred in Study ITSI (T1D, CSII) or in the clinical pharmacology studies.

Hypoglycaemia

In the three Phase 3 studies, the rate and incidence of severe hypoglycaemia were overall low. In T1D, the incidence of severe hypoglycaemia in the ITRM study was for LY900014, n=25 (5.5%), Humalog, n=25 (5.7%), and LY900014+20, n=15 (4.6%). In the CSII study ITSI, there was one episode of severe hypoglycaemia and one episode of potential severe hypoglycaemia in both Humalog and LY900014 groups (in total, 4). In the T2D study ITRN, there were 6/337 reports of severe hypoglycaemia in the Humalog group and 3/336 in the LY900014 group. Neither observed severe hypoglycaemic event rates nor SAE reports on hypoglycaemia differed overall between study groups in any of the analysed populations.

In the hypoglycaemia event surveillance during MMTT in study ITRM (T1D), the rate and incidence of all documented hypoglycaemia was similar in the Humalog group and the LY900014+20 group, and slightly lower in the LY900014 group than in the other groups. Slightly more non-nocturnal hypoglycaemias (both with BG <3.0 mmol/L and <3.9 mmol/L) were seen in LY900014+20/LY900014 comparison in T1D patients in ITRM. The rate and incidence of both documented symptomatic and documented symptomatic and asymptomatic post-meal hypoglycaemia were smaller in LY900014 group compared to Humalog group at >4 hours. On the other hand, the incidence and rate of documented symptomatic hypoglycaemia during the early post-meal period was higher in the LY900014 group than in the Humalog group. The postprandial administration of LY900014 (LY900014+20) caused slightly more post-meal hypoglycaemia than premeal administration of LY900014. Overall, hypoglycaemia caused by post-meal administration of LY900014 was in the same range as for Humalog. However, it is recommended that only if necessary in

certain situations, e.g. when there is uncertainty about the meal intake, Liumjev can be administered up to 20 minutes after starting the meal.

In ITRN T2D patients, higher documented symptomatic hypoglycaemia rate (with BG <3.0 mmol/L) was observed in the LY900014 group compared to the Humalog group: event rate/year (LSM [SE]) was 2.21[0.32] vs. 1.34[0.16] for LY900014 and Humalog, respectively. Also higher rate and incidence of non-nocturnal hypoglycaemia (with BG ≤3.9 mmol/L) was observed in the LY900014 group compared to the Humalog group during the first 4 hours post-meal. Only after 4 hours post-meal, higher rates of symptomatic and asymptomatic hypoglycaemia were observed in the Humalog than in LY90014 group. The observed pattern of post-meal hypoglycaemia rates and incidence in the T2D patient population are suggestive of a trend towards earlier hypoglycaemic events with LY900014 and later hypoglycaemic events with Humalog. This reflects the time-action profile of the insulin formulation as has been noted with other insulin formulations as well. As the patient needs to be aware of the timing of potential hypoglycaemic episodes, information is included in the planned prescribing information, in both the SmPC and the PIL, with a warning in PL currently reading as follows: "Liumjev starts to lower blood sugar faster than some other mealtime insulins. If hypoglycaemia occurs, you may experience it earlier after an injection of Liumjev. If you often have hypoglycaemia or have difficulty recognising it, please discuss this with your doctor."

In ITSI (T1D, CSII), the rate and incidence of all documented hypoglycaemia, documented symptomatic hypoglycaemia, and non-nocturnal hypoglycaemia were higher in the LY900014 group compared to the Humalog group. Documented symptomatic post-meal hypoglycaemia rate was also higher in the LY900014 group compared to the Humalog group. Based on continuous glucose monitoring (CGM), however, contradictory data regarding hypoglycaemia was retrieved in T1D patients. During CSII in ITSI, the time spent overall in hypoglycaemia was markedly shorter in subjects belonging to the LY900014 group instead of Humalog group. During the 24-hour period the differences, during the first day of infusion set wear, were the following: <2.8 mmol/L (LSM): LY900014, 9.55 minutes; Humalog, 17.97 minutes; <3.3 mmol/L (LSM): LY900014, 28.74 minutes; Humalog, 42.87 minutes, and ≤3.9 mmol/L (LSM): LY900014, 69.18 minutes; Humalog, 95.35 minutes. Similarly, in the ITRM CGM substudy, the results on the analyses of time in hypoglycaemia demonstrated that LY900014 was associated with somewhat less time in hypoglycaemia in comparison with Humalog.

As an overall conclusion on hypoglycaemic events, the rates of severe hypoglycaemia or nocturnal hypoglycaemia did not differ between LY90014 and Humalog. Overall incidence and rate of hypoglycaemic events was similar in T1D patients administered Humalog or LY900014; premeal administration of LY90014 was more beneficial in terms of hypoglycaemia than post-meal administration. In T2D, the incidence and rate of documented hypoglycaemia was slightly higher with LY90014. In both T1D and T2D, the timing of hypoglycaemic events followed the time-action-profile of LY900014 and Humalog: in the early post-meal period, more hypoglycaemia was noted with LY900014, and in the late (>4 hour) post-meal period, more hypoglycaemia occurred with Humalog. In contradiction with hypoglycaemia results obtained by SMBG in the ITSI study (T1D patients using insulin pump), CGM results indicate less hypoglycaemic events with LY90014 administered preprandially vs. Humalog. It is acknowledged that CGM yields more comprehensive data than SMBG. However, the clinical relevance of this finding is not known.

Unit-to-unit interchangeability of LY900014 and Humalog is supported by the AUC of lispro with both products. Nevertheless, the time-action profile of LY900014 results in more rapid onset of action and slightly higher peak concentration of insulin than seen for Humalog, which should also be taken in account when switching from other mealtime insulin to LY900014, with individual monitoring and surveillance by the treating physician.

Immunogenicity

Close to half of T1D patients had detectable ADA at the beginning of the 8-week lead-in period of ITRM (LY900014, 47.8%; LY900014+20, 49.8%; Humalog, 44.2%). The proportion of subjects with treatment-emergent anti-insulin lispro antibodies (TEADA) at any time point from Week 0 to Week 26 was similar across study arms: LY900014, 33.8%; LY900014+20, 31.5%; Humalog, 32.0%. At Week 52, however, the proportion of subjects with TEADA was 11.8% in the Humalog group and 15.6% in the LY900014 group due to higher proportion of subjects with treatment-induced ADA. At safety follow-up visit, the difference had decreased: proportion of TEADA-positive subjects was 10.9% in the Humalog and 13.2% in the LY900014 group.

26/49 of T1D patients in ITSI (CSII study) had TEADA, however, in 9 patients antibodies returned to baseline level at the last postbaseline visit.

In Study ITRN (T2D), about one third of subjects had detectable ADA at the beginning of the 8-week lead-in period (LY900014, 34.6%; Humalog, 34.4%). Overall, at any time during the study (including the safety follow-up visit), the proportion of patients with TEADA was higher in the LY900014 group compared with the Humalog group (LY900014, 34.6%; Humalog, 27.0%; p=0.037). However, the groups did not relevantly differ any more at safety follow-up visit, as in part of the subjects, elevation of ADA was transient.

Most patients who developed TEADA had low percent binding values and about 90% of ADA-positive patients in all Phase 3 studies were cross reactive to native insulin. The ADA percent binding levels were slightly higher in the Humalog group at earlier post randomization timepoints in both T1D and T2D patients. During the long-term follow-up, this difference in ADA levels in patients with TEADA disappeared. In ITRM (T1D), a slight decrease in efficacy was noted at 1 hour in TEADA-positive vs. TEADA-negative subjects without effect on overall glycaemic control. There was also a small difference in prandial/total insulin dose ratio between TEADA positive and TEADA negative subjects in the LY900014 arm of ITRM. In T2D, no effect on glycaemic control by TEADA was observed. Long-term follow-up of immunogenicity in T1D patients did not reveal any relevant effect of immunogenicity on efficacy or safety.

The most common SAEs in ITRM, ITRN and ITSI were hypoglycaemia SAEs. No differences in serious hypoglycaemia events were seen between the study groups in ITRM, ITRN and ITSI.

Two SAEs of severe hypoglycaemia events were reported in studies evaluating insulin pump safety. The events were considered not related to study treatment

Hypersensitivity reactions

In Study ITRM (T1D) overall, 69 patients (5.6%) experienced ≥1 treatment-emergent systemic hypersensitivity reaction by broad search terms and 30 patients (2.5%) by narrow search terms. By Week 26, the proportion of patients with potential systemic hypersensitivity reactions was higher in LY900014-treated patients with TEADA, but lower in Humalog-treated patients with TEADA (LY900014, n=6 [3.9%]; LY900014+20, n=5 [4.9%]; Humalog, n=0) compared to patients without TEADA (LY900014, n=6 [2.0%]; LY900014+20, n=4 [1.8%]; Humalog, n=8 [2.7%]) by Week 26. From randomisation to Week 52, the number of subjects with potential treatment-emergent systemic hypersensitivity reactions was evenly distributed (total 36, 18 subjects in both Humalog and LY900014 groups, narrow definition of MedDRA search terms). Of these, 14 and 9 were TEADA-negative and 2 and 8 TEADA-positive in the Humalog and LY900014 arms, respectively. In Study ITRN (T2D), similar percentages of LY900014- and Humalog-treated patients with TEADA (LY900014, 2 [1.7%]; Humalog, 2 [2.2%]) and without TEADA (LY900014, 4 [1.8%]; Humalog, 6 [2.4%]) reported potential systemic hypersensitivity reactions. The events were too scarce for statistical comparison.

In phase 3 studies, injection site reaction TEAEs were remarkably more common in the LY900014 groups compared to the Humalog groups: in ITRM and ITRN, 30 (2.7%) vs 1(0.1%) (p<0.0001) for LY90014 and Humalog, respectively. None of these events were reported as SAEs. In Study ITSI, the incidence of

potential treatment-emergent infusion site reactions (composite term) was markedly higher for LY900014 compared with Humalog (LY900014, 19 patients [38.8%]; Humalog, 6 patients [12.5%]; p=0.006). All events were mild (98.2%) or moderate (1.8%) in severity, none led to discontinuation, and all resolved during the study with no change to dosing of study drug.

Also in clinical pharmacology studies, erythema was reported almost 10-fold as often after LY900014 SC doses as after Humalog SC doses. Erythema events were, however, very mild. According to injection site assessments in studies evaluating treprostinil, the concentration of treprostinil did not appear to be in relation to injection site reactions, nor did that of sodium citrate. There were, however, between-group differences highlighting erythema in subjects/patients both in PK and phase 3 studies.

No consistent association was observed between local hypersensitivity reactions and TEADA, hence, immunogenicity does not explain the 10-fold difference in injection/infusion site reactions with LY900014 compared to Humalog.

Systemic hypersensitivity reactions were too scarce for statistical analysis of comparative frequency.

No concern arose about laboratory parameters, vital signs or ECG findings. As a vasodilator, treprostinil might lower blood pressure and cause tachycardia, but even in the PK study evaluating treprostinil, no such effects were seen.

2.6.2. Conclusions on the clinical safety

The Applicant has provided a detailed and careful assessment of hypoglycaemic episodes. In both T1D and T2D patients, the hypoglycaemia events occurred more rapidly with LY900014 after the meals compared to Humalog; in Humalog groups, the hypoglycaemia events occurred closer to 4 h post-meal and in LY900014 groups starting right after the meals. This is in line with the nature of the new fast-acting product. In T2D, the incidence and rate of documented hypoglycaemia was slightly higher with LY900014.

The rate of severe hypoglycaemia did not differ between LY900014 and Humalog. Overall incidence and rate of hypoglycaemic events was similar in T1D patients administered Humalog or LY900014 as MDI regimen; less with premeal administration of LY900014 vs. post-meal administration of LY900014. Early post-meal hypoglycaemia was more frequent with LY900014 and late post-meal hypoglycaemia with Humalog. There was a very small difference in diurnal timing in the MDI study with T1D subjects (ITRM): slightly more nocturnal hypoglycaemia with Humalog and slightly more non-nocturnal hypoglycaemia with LY900014. In the CSII study ITSI, slightly more hypoglycaemia was observed with LY900014 vs. Humalog, except for the CGM results in T1D patients that indicated less hypoglycaemic events with LY900014 administered preprandially. The decrease in especially glucose levels <2.8 mmol/L could help in preservation of adrenergic alert symptoms of hypoglycaemia if the CGM results are considered more reliable than hypoglycaemia results collected by other means.

Some severe hypoglycaemia events - categorised as SAEs - were seen in the data, with no difference between study groups. The number of other SAEs was low.

Erythema was reported remarkably more often in the LY900014 groups than in the Humalog groups throughout the studies, but the number of events was, however, low, and the cases were generally very mild. Based on the safety data from PK studies, treprostinil or citrate did not appear to be in relation to injection site reactions. No obvious relation was seen between TEADA and local hypersensitivity reactions. Systemic hypersensitivity reactions were too scarce for statistical comparison between TEADA-positive and –negative subjects.

At baseline, close to half of T1D subjects and one third of T2D had ADA. Most of the ADA-positive patients were cross-reactive to native insulin. Evolution of treatment-emergent ADA (TEADA) was closely similar

in T1D patients in Humalog and LY900014 groups; however, at Week 52 there were more subjects with TEADA in the LY900014 group. In T2D patients, more subjects developed TEADA in the LY900014 group (34.6%) than in the Humalog group (27.0%).

On the other hand, the ADA percent binding levels, though overall low, were slightly but significantly higher in the Humalog group at early time points in both T1D and T2D subjects. Since part of the elevation in ADA levels was transient, the difference between the Humalog and LY90014 groups decreased during the safety follow-up and was no more observed during the ADA follow-up period of either ITRM (T1D) or ITRN (T2D) studies.

There was a statistically significant treatment-by-TEADA status interaction for bolus: total insulin dose ratio in T1D subjects, and further review showed that patients with positive TEADA status treated with LY900014 had a slightly but statistically significantly lower bolus: total insulin ratio than patients treated with Humalog. TEADA-positive T1D subjects also had a slightly attenuated effect of LY900014 on postprandial glucose at one hour but no more at 2 hours. These small differences, seen only in T1D subjects, are not deemed clinically relevant. TEADA did not affect HbA1c levels or total daily insulin doses in either T1D or T2D subjects. Development of TEADA was not related to safety outcomes.

The CHMP considers the safety profile acceptable.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities. Routine pharmacovigilance is considered sufficient for this product.

Risk minimisation measures

As there are no important risks or missing information included as part of the safety specification of the RMP, routine risk minimisation measure is considered sufficient for this product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 9.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

However, based on the difference in the pattern of hypoglycaemias between the new lispro formulation and the already approved formulations, the CHMP is of the opinion that the already existing entry in the EURD list for insulin lispro needs to be amended as follows (upon authorisation of Liumjev): the PSUR cycle for the medicinal product should follow a yearly cycle. The next data lock point will be 2020-04-30.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Liumjev (insulin lispro) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

2.10. Assessment for the purpose of Art 82(1) of Regulation EC No 726/2006 (duplicates)

Background for full stand-alone MA for Liumjev

The Applicant claimed that there are distinct and clinically relevant differences between the two formulations (i.e. Humalog and Liumjev) which mandate different prescribing information and trade name for Liumjev and that therefore these two products would not fall within the scope of Article 82(1) of Regulation EC No 726/2004and that these differences include:

With regards to the efficacy

The data provided on Liumjev show that, compared to Humalog, there is a shift in the PK/PD profile resulting in an earlier onset of the glucose-lowering effect while the total glucose-lowering effect is similar. In the pivotal phase 3 studies, statistically significant lowering of the post-prandial glucose (PPG) increment with Liumjev compared to Humalog in patients with T1D and T2D was documented after 26 weeks. The magnitude of this effect was highly significant and clinically relevant in TD1 (−1.55 mmol/L at 1 hour and −1.73 mmol/L at 2 hours post-meal), with less pronounced but still clinically relevant effect in T2D (−0.67 mmol/L at 1 hour and -0.98 at 2 hours post-meal. This improved post-prandial control with LY900014 compared with Humalog was maintained up to 52 weeks in T1D subjects. The mean daily post-meal glucose excursions from premeal to 1 hour post-meal at Week 52

were the following: LSMean difference −0.79 mmol/L (95% CI −1.11, −0.48, p<0.001); and from premeal to 2 hours post-meal: LSMean difference −0.46 (95% CI −0.78, −0.15, p=0.004).The difference in PPG lowering effect is reflected in the SmPC.,

Literature supports that increased PPG is important for glycaemic control overall and the relative impact of post-prandial glycaemia increases when HbA1c decreases. Potential independent role of PPG in the development of macrovascular and microvascular complications is still under debate, as long-term controlled data on PPG is scarce, and the hypothesis of importance of PPG is supported by epidemiological data mostly. Therapeutic guidelines recommend lowering of PPG in T1D as part of compensation for lack of physiological postprandial insulin secretion spikes. In T2D, post-prandial glycaemia should be targeted at least in patients unable to reach desired glycaemic control only by targeting fasting glucose.

The MDI studies ITRM (TID) and ITRN (T2D) were conducted as treat-to-target studies. As expected, there was no statistically significant difference in HbA1c at week 26 in either study. Both studies met the primary endpoint of non-inferiority to Humalog in glycaemic control.

Thus, it is agreed that Liumjev has shown statistically and clinically significant in 1h and 2h post-meal effect on lowering of PPG due to the two different excipients and can be considered as having significant difference regarding efficacy, compared to Humalog**,** and falls consequently outside of the scope of Article 82 (1) of Regulation EC No 726/2004 (i.e duplicate MA).

With respect to safety,

There was a difference in the pattern of hypoglycaemic episodes in T2D (ITRN study). There was a significantly higher rate of documented symptomatic hypoglycaemia (BG <3.0 mmol/L) in the LY900014 group than in the Humalog group overall (LSM Mean 2.21 versus 1.34 events/year; ratio [95% CI] =1.64 [1.14, 2.38]); ≤2hours post-meal (1.23 vs. 0.66, RR=1.86 [1.08, 3.20]); ≤4hours post-meal (1.77 vs. 0.98, ratio=1.81 [1.19, 2.74]); and >2 to ≤4hours post-meal (0.54 vs. 0.33, ratio=1.71 [1.09, 2.69]) for Liumjev compared to Humalog.

In T1D (ITRM), on the other hand, after 4 hours post-meal the incidence of hypoglycaemic events was significantly larger in Humalog group compared to Liumjev from randomisation to week 26: rate/year(SE) for Humalog: 26.00(1.94), LY90014: 19.89(1.38), ratio [95% CI] 0.76 [0.63, 0.93].

Over the controlled treatment period from randomisation to end of the 56-week controlled period, rate (events/patient/year, LSM (SE)) and incidence (%) of documented symptomatic hypoglycaemia (BG≤3.9 mmol/L) was closely similar as observed for the 26-week period. The rate at >4 hours from meal was in the Humalog group significantly higher than in the LY900014 group: 22.02/year, 77.2% vs. 16.75/year (RR 0.76, p= 0.0009). The incidence of hypoglycaemia at >4 hours postmeal was 77.2% in the Humalog group vs. 75.6% in the LY900014 group. Results were similar when using the more stringent threshold of 3.0 mmol/l for hypoglycaemia: incidence 43.4% and 40.1% in Humalog and LY900014 groups respectively, and rate 2.20 vs. 1.52, respectively (RR 0.69, p=0.023) at >4 hours post-meal. Using the 3.0 mmol/L threshold, there was additionally a statistically significant difference in early post-meal hypoglycaemia at ≤1 hour post-meal (from randomisation to week 56) with higher rate and incidence in the LY900014 group: rate 0.77 vs. 0.63 and incidence 29.7 % vs. 21.7 % (RR 1.22, p = 0.007) in the LY900014 vs. Humalog group. However, the overall rate and severity of events was comparable between treatments. It has been reflected in the SmPC that hypoglycaemia may occur earlier after an injection/infusion of Liumjev compared to other mealtime insulins.

In the insulin pump study ITSI (T1D, there was a higher rate of non-nocturnal hypoglycaemia (BG<3.9 mmol/L) in the LY900014 than in the Humalog group (weeks 4-6 of the 6-week period): mean (SD): 42.9(57.66) for LY900014 versus 66.85(82.24) for Humalog.

Therefore, it is agreed, that the difference in timing of hypoglycaemic episodes due to the different excipients can be considered a significant difference in safety between Liumjev and Humalog, and consequently Liumjev falls outside of the scope of Article 82 (1) of Regulation EC No 726/2004 (duplicate MA).

As a conclusion, regarding the Applicant's claim of significant differences in safety or efficacy in Liumjev vs Humalog for the purpose of Art 82(1) of Reg (EC) No 726/2004 and in view of the EC note on Handling of Duplicate Marketing Authorisation Applications Ares(2011)1044649, CHMP considers that Liumjev shows significant differences in terms of safety and efficacy due to different excipients versus Humalog in view of the difference in the timing of hypoglycaemia and significantly improved PPG (associated with differences in PK/PD).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication of LY900014 is treatment of diabetes in adults.

The product is intended for use as mealtime insulin or for CSII.

In LY900014, addition of two excipients has rendered the insulin time-action profile to shift to the left when compared with Humalog: enhanced absorption of insulin lispro through increased local vasodilation, due to the addition of a microdose of treprostinil as an excipient in the formulation; and speeding absorption of insulin through enhanced local vascular permeability, which is achieved by addition of the excipient sodium citrate in the formulation. The quicker time-action profile is intended to help postprandial glycaemic control in patients who cannot for various reasons inject prandial insulin in advance of the meal or cannot predict the amount of insulin needed for the meal beforehand.

3.1.2. Available therapies and unmet medical need

Mealtime insulin or prandial insulin are used for subcutaneous bolus injection at meals for controlling postprandial glucose excursions. They can also be used in external insulin pump for continuous subcutaneous insulin infusion to cover both basal and bolus insulin. If needed, they can be used intravenously, too, as the faster time-action profile is linked to faster absorption; however, one in circulation, they act similarly to human insulin.

Rapid-acting insulin analogues, first of which was insulin lispro, were developed to enable efficient postprandial glucose control. Compared to regular human insulin, insulin lispro has a more rapid onset, higher peak and shorter duration of action, which better fits for controlling postprandial glucose excursions. The daily insulin regimen is adjusted individually for every patient. Prandial insulin boluses are titrated based on glucose monitoring and carbohydrate content of the meal to achieve glycaemic targets. Even with rapid-acting insulin analogues, efficient control of postprandial glucose elevation requires preprandial administration of insulin, optimally 15 to 20 minutes before the start of a meal, so that the peak insulin concentration occurs concomitantly with postprandial glucose elevation. In many instances, appropriate timing is not feasible; e.g. if the patient cannot anticipate the time of meal or amount of ingested carbohydrates. Sometimes faster cessation of action is also beneficial, e.g. if the patient needs to exercise a few hours after injecting insulin.

In clinical practice situations, when prandial insulin needs to be injected during or after the meal instead of before meal, are common. Hence, there is need for more rapid insulin formulations than current rapid-acting analogue insulins such as lispro (Humalog, Liprolog, Insulin lispro Sanofi), aspart (NovoRapid), or glulisine insulin (Apidra). There already is on the market one ultra-rapid mealtime insulin product, Fiasp-insulin: insulin aspart formulation in which the addition of nicotinamide (vitamin B3) results in a faster initial absorption of insulin.

The purpose of the development of LY900014 has been to provide a faster glucose-lowering effect that mimics more closely the physiological carbohydrate absorption profile and mealtime insulin response than the currently available insulin lispro products.

3.1.3. Main clinical studies

In addition to 22 clinical pharmacology PD/PK-studies, two Phase 3, prospective, randomized, outpatient, multinational, multicentre, parallel, active-controlled studies with a multiple daily injection (MDI) regimen were conducted to establish the efficacy of LY900014 to improve glycaemic control: Study I8B-MC-ITRM (ITRM) in patients with T1D, and Study I8B-MC-ITRN (ITRN) in patients with T2D. A third Phase 3 study, Study I8B-MC-ITSI (ITSI), a prospective, randomized, double-blind, crossover comparison evaluating compatibility and safety of LY900014 and Humalog with an external continuous subcutaneous insulin infusion (CSII) system in adult patients with T1D.

3.2. Favourable effects

Pharmacodynamic data show an earlier onset of action with LY900014 compared to Humalog. The total exposure to insulin lispro (AUC0-∞) is similar between LY900014 and Humalog. Due to more rapid absorption, C_{max} is slightly higher for LY900014 compared with Humalog following a SC injection. A 14% increase in C_{max} was estimated in a meta-analysis of four clinical studies. This small difference is not expected to have clinical consequences.

Comparable pharmacokinetics and pharmacodynamics between LY900014 200 U/mL and LY900014 100 U/mL formulations was demonstrated in a euglycaemic glucose clamp study in healthy subjects.

In the two Phase 3 multiple-daily-injection regimen studies in TD1 and TD2 patients LY900014 was non-inferior compared to Humalog for change in HbA1c from baseline to Week 26. The changes were for ITRM, T1D patients, [-0.08 (-0.16, 0.00)] and ITRN, T2D patients, [-0.08 (-0.16, 0.00)]. Non-inferiority was confirmed by analyses according to efficacy and ITT estimands.

LY900014 treatment demonstrated consistently better PPG control compared to Humalog. Studies in both T1D and T2D met 2 prespecified multiplicity objectives; when administered prior to the start of the meal, LY900014 was superior to Humalog in controlling 1-hour and 2-hour PPG excursions during mixed meal tolerance test. Results from the 10-point SMBG profile data support improved PPG control in T1D patients (IRMN) with LY900014 (ITT estimand). ITRM, 1-hour difference: -1.55 mmol/L (-1.96, -1.14) and 2-hour difference: -1.73 mmol/L (-2.28, -1.18). The respective results for T2D were at 1 hour: -0.66 (-1.01, -0.30) mmol/L (ITRN). Closely similar results were obtained in the efficacy estimand analyses. Additionally, PPG lowering was statistically significantly better with LY900014 compared to Humalog during the entire 4-hour MMTT ($iAUC_{0\text{-}4\ hours}$) in T1D patients and in T2D patients. Improved postprandial control with LY900014 in comparison with Humalog was maintained up to 52 weeks in T1D subjects.

In Study ITRM(T1D), post-meal LY900014+20 was noninferior to Humalog for glycaemic control as measured by change in HbA1c, but change in HbA1c was statistically significantly higher in LY900014+20. In T2D patients, no difference in HbA1c between study groups was seen.

Support for differential effect on glucose excursions and variability were obtained by SMBG, continuous glucose monitoring, assessment of incremental iAUC during MMTT and by measuring fasting glucose. iAUC was in T1D patients (ITRM) statistically significantly lower in LY900014 versus Humalog at all time intervals during MMTT (0-30 minutes, 0-1 hour, 0-2 hours, 0-3 hours, and 0-4 hours); statistically significantly higher in LY900014+20 group versus Humalog at 0-30 minutes and 0-1 hour, but similar at 0-2 hours, 0-3 hours, and 0-4 hours; and statistically significantly higher in LY900014+20 versus LY900014 at all time intervals (0-30 minutes, 0-1 hour, 0-2 hours, 0-3 hours, and 0-4 hours).

In ITRM (T1D), fasting glucose (FG) values at week 26 in the MMTT were significantly lower in patients administered LY900014 either premeal (6.58 mmol/L) or post-meal (6.40 mmol/L) in comparison with

Humalog (7.20 mmol/L). No difference in FG was observed between LY900014 and Humalog groups in T2D patients (ITRN).

1,5-anhydroglucitol (1,5-AG) was measured in the Phase 3 studies as a marker of postprandial glycaemia, which has been implicated as risk factor for diabetic micro- and macrovascular complications. 1,5-AG levels increased (improved) from baseline to week 26 in T1D patients treated for 26 weeks with mealtime LY900014 and decreased in Humalog and LY900014+20 groups (study ITRM). However, regardless of lowering of PPG excursions, no similar improvement was observed in T2D patients or in the CSII study ITSI on T1D patients.

No difference was seen in the ITRM study (T1D) in the mean SMBG values (from all time points of day) at week 26 between preprandial LY900014 compared to Humalog. However, when postprandial and preprandial administration of LY90014 was compared, mean BG was statistically significantly lower in the LY900014 arm (8.93 mmol/L) versus LY900014+20 arm (9.27 mmol/L), p=0.011. Also in T2D (ITRN) mean PPG excursions during MMTT, were at week 26 statistically significantly lower with LY900014 compared to Humalog, at all time points from 30 minutes to 4 hours. SMBG demonstrated that PPG excursions from premeal to 1 and 2 hours post-meal daily mean was statistically significantly lower LY900014 compared to Humalog, at both time points.

Basal, bolus and total insulin doses were similar between study arms in both MDI studies. A similar increase in insulin doses was seen in both studies and all study arms.

The ITRM substudy with continuous glucose monitoring demonstrated that in T1D patients, time in target range [3.9 to 7.8 mmol/L] could be markedly different depending on prandial insulin formulation and timing of injection. At Week 26: LY900014 group was 40.8 minutes more time in range (p=0.015) during daytime with no other differences noted for night-time or 24-hour periods versus Humalog. No statistically significant treatment differences were seen in comparison between LY900014+20 versus Humalog. However, in comparison with preprandially injected LY900014, patients who injected LY900014 postprandially (LY900014+20), were 57.0 minutes less time in range (p=0.001) during daytime and 67.7 minutes less time in range (p=0.004) during the 24-hour period.

Similar results were obtained from CGM in the ITSI study (T1D, CSII). Patients treated with LY900014 spent more time with glucose in the target ranges on both Day 1 and Day 3 of infusion set wear when compared to patients treated with Humalog; however, ITSI was not powered to show statistical differences in efficacy endpoints.

3.3. Uncertainties and limitations about favourable effects

In T2D, the benefits achieved by using LY900015 preprandially vs. Humalog preprandially are not as strong as in T1D. Whereas the 2-hour glucose excursion decreases ~1.7 mmol/L in T1D patients, the corresponding decrease in T2D patients is only -0.96 mmol/L. In T2D the mean improvement in PPG control did not reflect to overall glycaemic control, either.

All other measures of glycaemic variability show more moderate effect difference between Humalog and LY900014 arms, too. E.g., the SMBG curve obtained in ITRM only differs in the values after morning meal, not after lunch of dinner. No reason for this diurnal phenomenon is given in the dossier.

The health outcome measures used in the Phase 3 trials did not demonstrate any difference between study arms. It is known that high glucose values may cause tiredness and mood changes in addition to thirst, increased urination etc. Obviously, the used methods are not sensitive in capturing feelings of wellbeing.

The instructions on administering glucose in the Phase 3 studies included immediately premeal injections of Humalog and Ly900014. Patients in the LY900014+20 group were instructed to take the insulin 20 minutes after the meal. Hence, there was no comparison to Humalog administered 15 minutes prior, which would be the optimal dose regarding the time-action profile of Humalog. In addition, no comparison is available for Humalog administered post-meal (apart from one PD-study).

There was a slight difference in HbA1c in favour of LY900014 in the ITRM study, however, the secondary endpoint of superiority in terms of HbA1c was not met. In T2D patients, HbA1c was also similar in both groups. These results might be interpreted as an argument against the importance of postprandial control to overall glycaemic burden. However, no marked changes in HbA1c can be expected in treat-to-target studies. Individual optimisation of insulin treatment, snacking, exercise, etc. affect al study arms and attenuate the differences between groups.

3.4. Unfavourable effects

There was no overall difference in the risk of hypoglycaemic events between Humalog and LY900014. However, clinically significant differences were seen in the pattern of timing of hypoglycaemic events.

In T1D (ITRM, MDI regimen), documented symptomatic hypoglycaemia (<3.0 mmol/L) rates, adjusted per year, were overall numerically slightly higher for Humalog than LY900014, whereas the rate was overall similar between LY900014+20 and Humalog. The rates for Humalog, LY900014 and LY900014+20 from randomisation to week 26 (LS Mean) were 7.35, 6.71, and 7.75; all documented hypoglycaemia 13.48, 12.46, and 14.24; non-nocturnal hypoglycaemia 8.88, 8.13, and 9.85; and nocturnal hypoglycaemia 1.75, 1.25, and 1.24, respectively. No difference in overall hypoglycaemia ranges were seen with the threshold of ≤3.9 mmol/L, either.

There were some differences noted in the timing of hypoglycaemic events. In T1D (ITRM), documented symptomatic hypoglycaemia rate from baseline to Week 26 (BG<3 mmol/L, adjusted for 1 year, LS Mean) in the late post-meal period >4 hours post-meal was lower in the LY900014 group (19.89) compared to Humalog (26.00), with ratio [95%CI] 0.76[0.63, 0.93]. Rates were higher with the LY900014+20 compared to Humalog from 2 to 4 hours post-meal for BG 3.0 mmol/L and lower with LY900014+20 compared to LY900014 during the postprandial period from 1 to 2 hours after meals for BG ≤3.9 mmol/L. Overall, slightly more hypoglycaemia occurred when LY900014 was administered post-meal than premeal. As a consequence, post-meal administration of LY900014 should not be used routinely, but only when necessary e.g. if the carbohydrate consumption during the meal cannot be anticipated.

In T2D (ITRN), the respective hypoglycaemia (<3.0 mmol/L) rates for Humalog and LY900014 (LS Mean) were the following: documented symptomatic hypoglycaemia 1.34 and 2.21, ratio 1.64 [95% CI 1.14, 2.38]; all documented hypoglycaemia 7.43 and 7.57; non-nocturnal hypoglycaemia 3.20 and 3.92; and nocturnal hypoglycaemia 0.53 and 0.68, respectively. Furthermore, hypoglycaemic (<3.9 mmol/L) rates (from baseline to Week 26, adjusted for 1 year) were higher with mealtime LY900014 than Humalog in the postprandial periods ≤1 (4.71 vs. 2.78, ratio 1.75 [1.09, 2.83]); ≤2 (7.90 vs. 4.34, ratio 1.82 [1.31, 2.54]), ≤4 (12.91 vs. 8.39, ratio 1.54 [1.19, 1.99]), and >1 to ≤2 (3.21 vs.1.56, ratio 2.06 [1.37, 3.09]) hours post-meal. The difference in documented symptomatic hypoglycaemic events (<3.0 mmol/L) results were driven by hypoglycaemic events in the postprandial period. The observed pattern of post-meal hypoglycaemia rates and incidence, especially increase in early post-meal hypoglycaemia, reflects the time-action profile of LY900014 vs. Humalog. A warning is included in the SmPC and PL of the faster action of the insulin and consequent risk of earlier hypoglycaemia with LY900014. It is recommended in the PL that a patient who has often hypoglycaemia or difficulty recognising it should discuss this with the doctor.

No difference among treatments was seen in severe hypoglycaemia rates in the MDI studies. In T1D (ITRM), the mean rate of severe hypoglycaemia from baseline to Week 26 was 18.48, 17.04, and 21.15 in the Humalog, LY900014, and LY900014+20 arms, respectively. Incidence of hypoglycaemic episodes was 25/442 (5.66%), 25/4521 (5.54%), and 15/329 (4.56%), respectively. In T2D, the mean rate of severe hypoglycaemia in Humalog and LY900014 groups was 4.15 and 2.37 and incidence 6/336 (1.78%) and 3/336(0.89%), respectively.

There were more than tenfold more patients in the All LY group, compared with the Humalog group, with at least 1 potential treatment-emergent injection site reaction AE using the customized MedDRA search (30 [2.7%] and 1 [0.1%]; p<0.0001). None of the events were reported as SAEs.

The most frequently (≥3 All LY patients) reported SAEs were hypoglycaemia, pneumonia, cellulitis, and chronic obstructive pulmonary disease. No statistically significant treatment differences were observed, and no clinically important differences were observed between patients in the All LY and Humalog groups with respect to SAEs.

The most frequently reported events, and also reported at a statistically significantly higher incidence in the All LY group were: injection site pain (All LY, 13 [1.2%], 17 events; Humalog, 0); Injection site reaction (All LY, 12 [1.1%], 20 events; Humalog, 1 [0.1%], 1 event). All events were mild or moderate in severity.

At week 26 in study ITRN, the double-blind TEADA-positivity increased more in T2D patients in the LY900014 than in the Humalog arm. This phenomenon was not seen in T1D; on the other hand, a larger proportion of T1D patients were ADA positive already at baseline. The proportions of subjects with ADA decreased during follow-up. In T1D patients at Week 52, there were more subjects with TEADA in the LY900014 group than in the Humalog group. This difference disappeared during the safety follow-up period. There were slightly higher levels of antibodies (% binding) in the Humalog arm in T1D and T2D patients; the difference was statistically significant in earlier phases of the studies ITRM and ITRN and no more present at end of ADA follow-up period of either study.

ADA positivity may have been linked with local and systemic hypersensitivity reactions, as most of these reactions occurred to ADA positive subjects. However, incidence of treatment-emergent ADA was not important for these reactions, since the overall numbers of patients with ≥1 potential treatment-emergent systemic hypersensitivity reactions or injection site reactions was similar in TEADA-negative and TEADA-positive T1D and T2D patients. However, the great majority of ADA positive patients did not have any local irritation.

In study ITSI, there was no difference between study arms in the primary endpoint, the rate or incidence of infusion set failures during the 6-week treatment period.

3.5. Uncertainties and limitations about unfavourable effects

The mechanism behind the increased rate of injection and infusion site reactions with LY900014 vs. Humalog is not known for certain. The Applicant suggests that the local vasodilatation by treprostinil and enhanced permeability by citrate could both be partly responsible for this difference; or these compounds could *per se* cause the irritation. Treprostinil is the active substance in Remodulin that is known to cause injection site reactions; and citrate has been associated with injection site pain in other injectable products. Overall, the injection site reactions were mild or moderate in severity, resolved without sequalae, and only one patient in the Phase 3 studies discontinued study medication due to injection site reaction.

In contradiction with hypoglycaemia results obtained by SMBG in the ITSI study (T1D patients using insulin pump), CGM results indicated not only lower glycaemic variability but also less hypoglycaemic

events with LY90014 administered preprandially vs. Humalog. Similar results were seen in the CGM substudy of the ITRM (MDI regimen, T1D patients). If true, the lowering of hypoglycaemic events (especially BG<2.8 mmol/L) could be important for T1D patients e.g. in regard to preservation of adrenergic alert symptoms of hypoglycaemia. Even though CGM is a more comprehensive and hence a more reliable method for surveillance than SMBG, the clinical relevance of this finding is uncertain.

No data are available for diabetic subjects with advanced autonomic neuropathy, especially gastroparesis. Gastroparesis is defined as delayed or disordered gastric emptying in the absence of mechanical obstruction (Krishnasamy et al 2018). For patients with delayed gastric emptying a less fast-acting mealtime insulin or later administration of mealtime insulin would probably be advisable to avoid early postprandial hypoglycaemia. The Applicant was requested to consider adding a warning on this in the SmPC. However, the same risk concerns all mealtime insulins and gastroparesis is not caused by insulin. Hence, it is agreed with the Applicant that this warning is not absolutely necessary.

It is uncertain if the name of the Liumjev KwikPen Junior presentation carries a risk for off-label use in paediatric population, since "Junior" might be associated with paediatric patients. The potential risk of increased hypoglycaemia in children that may accompany off-label use cannot yet be determined, since paediatric development is still underway and only preliminary results are available. Therefore, the Applicant has confirmed their commitment on the following:

> The potential for medication errors and off-label use in the paediatric population linked to adverse reactions for Liumjev should be monitored, analysed and reported as part of the upcoming PSUSA for insulin lispro (covering all formulations for Humalog, Liprolog and (soon) Liumjev). Based on the analysis of the reported data as part of the upcoming PSUSA, the MAH should also discuss/propose whether further risk minimisation measure(s) are considered necessary at this stage.

3.6. Effects Table

The efficacy results in the Effects table are given according to the efficacy estimand analyses, similarly to the proposed Product Information. For clinical decisions on insulin doses for the individual patient the expected results when the product is in use are most important, i.e., efficacy estimand results instead of ITT estimand results, as the latter include also patients who discontinued treatment.

Table 34. Effects Table for LY900014 (Type 1 and Type 2 Diabetes Mellitus)

Effect	Short Description	Unit	LY900014	Humalog	Uncertainties/ Strength of evidence	References
Favourable Effects						
HbA1c T1D	Change in HbA1c from BL	% (mmol/mol)	-0.13 (-0.6)	-0.05 (-1.4)	Primary endpoint, treatment difference: -0.08[-0.16;1.8]$_{95\%CI}$. (-0.8[-1.7;0.0]) Non-inferiority confirmed	Tables 3.3.5.5 and 3.3.5.6
HbA1c T2D	Change in HbA1c from BL	% (mmol/mol)	-0.38 (-4.1)	-0.43 (-4.7)	Primary endpoint, treatment difference: 0.06[-0.05;0.16]$_{95\%CI}$. (0.6[-0.6;1.8]) Non-inferiority confirmed	Tables 3.3.5.5 and 3.3.5.6
1-hour PPG increment T1D	Change in 1-hour PPG increment from BL after meal test	mmol/L	-1.59	-0.04	Secondary endpoint, treatment difference of -1.55 mmol/L [-1.96; -1.14]$_{95\%CI}$. Superiority confirmed	Table 3.3.5.7

Effect	Short Description	Unit	LY900014	Humalog	Uncertainties/ Strength of evidence	References
1-hour PPG increment T2D	Change in 1-hour PPG increment from BL after meal test	mmol/L	-0.77	-0.11	Secondary endpoint, treatment difference, -0.66 mmol/L $[-1.01;-0.30]_{95\%CI}$. Superiority confirmed	Table 3.3.5.7
2-hour PPG increment T1D	Change in 2-hour PPG increment from BL after meal test	mmol/L	-1.93	-0.20	Secondary endpoint, treatment difference of -1.73 mmol/L $[-2.28;-1.18]_{95\%CI}$. Superiority confirmed	Table 3.3.5.7
2-hour PPG increment T2D	Change in 2-hour PPG increment from BL after meal test	mmol/L	-1.06	-0.09	Secondary endpoint, treatment difference, -0.96 mmol/L $[-1.41; -0.52]_{95\%CI}$. Superiority confirmed	Table 3.3.5.7
Unfavourable Effects						
Hypo-glycaemia T1D	All documented episodes (BG<3.0mmol/L) (week 0 to 26)	Rate/ Hypoglycaemia/year	LY 900014 12.46, LY900014 14+20 14.24	13.48	Other secondary objective Slightly favours preprandial LY90014 in comparison with Humalog and with postprandial LY900014.	Table 3.3.8.2
Hypo-glycaemia T2D	All documented episodes (BG<3.0mmol/L) (week 0 to 26)	Rate/ episodes/ year	7.57	7.43	Other secondary endpoint. No relevant difference.	Table 3.3.8.6
	Documented symptomatic episodes (BG<3.0mmol/L) (week 0 to 26)	Rate/ episodes/ year	2.21	1.32	Favours Humalog. Trend towards earlier hypoglycaemia is included in SmPC.	
Anti-insulin antibody formation T1D	ADA-positive at BL; treatment-emergent ADA at EOT(w26)	%	48.6; 32.8	44.2; 32.0	Tertiary/exploratory objective; no difference in TEADA	Table 3.3.8.7
Anti-insulin antibody formation T2D	ADA-positive at BL; treatment-emergent ADA at EOT(w26)	%	34.6; 30.7	34.4; 23.7	Tertiary/exploratory objective; more TEADA with LY900014	Table 3.3.8.7
Injection/ infusion site reactions in Ph3 studies*	Reported AEs	number (%) of subjects	30 (2.7)	1 (0.1)	Significantly more with LY900014 than Humalog	Section 3.3.8

*The composite term 'injection/infusion site reaction' included pain, itching, induration, erythema, and oedema at injection/infusion site.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Benefits of LY900045 in the treatment of T1D and T2D were robustly demonstrated as non-inferiority to Humalog in the change in HbA1c at 26 weeks was shown.

The major difference of LY900014 in comparison with Humalog is the time-action profile, which is shifted to the left; hence, the glucodynamic effect starts earlier and ends earlier. The other difference observed in the trials is increased number of local irritation at injection and infusion sites.

In T1D patients, a marked improvement in postprandial glycaemia is seen when LY900045 is injected prior to meal. In study ITRM, the mean decrease in 2-hour glucose value postprandially was 1.69 mmol/l, which can be considered clinically highly relevant. In T2D subjects, the reduction in postprandial 2-hour glucose was just below 1 mmol/L. What is the relevance of such a decrease in postprandial glucose excursion to an individual patient? Discrepant data are available on the importance of postprandial hyperglycaemia as risk factor for diabetic micro- and macrovascular complications. Current treatment guidelines from the EASD and ADA recommend targeting postprandial glucose in patients who cannot achieve adequate overall glycaemic control otherwise. The clinical relevance of the improvement in postprandial control in T2D is less obvious than in T1D. The Applicant was requested to discuss the observed differences in glycaemic control as regards onset of action and duration of action compared to Humalog; however, the Applicant could not define which patients with T1D and T2D are expected to specifically benefit from the faster onset of action of LY900014 compared with the currently marketed insulin lispro. In clinical practice, it is expected that patients chosen to use LY900014 would be the individuals with uncontrolled post-meal glucose excursions.

In ITRM (T1D), fasting glucose (FG) values at week 26 in the MMTT were significantly lower in patients administered LY900014 either premeal (6.58 mmol/L) or post-meal (6.40 mmol/L) in comparison with Humalog (7.20 mmol/L). These differences in FG were not expected, as the duration effect of the prandial insulin prior to evening snack does not extend to following morning. The finding might be speculated to be due to lower postprandial excursion after evening snack in the previous evening that is still reflected in the morning glucose level. No difference in FG was observed between LY900014 and Humalog groups in T2D patients (ITRN).

One of the measures of glucose variability in the Phase 3 studies was 1,5-AG, which is a known marker of postprandial glycaemia. Retrospective analyses from healthcare databases have implicated that 1,5-AG could be a predictor of cardiovascular disease and microvascular complications. In T1D patients there was a statistically significant improvement in 1,5AG in study ITRM in patients administered mealtime LY900015 vs. Humalog; no difference was noted in studies ITRN and ITSI. However, the issue if postprandial glycaemia is an independent risk factor or just part of the risk posed by overall glycaemic burden is currently unresolved. According to current treatment guidelines, the main target in treatment of hyperglycaemia is to achieve adequate glycaemic control without risk of serious hypoglycaemic events.

On the other hand, in T1D patients, flattening of glycaemic fluctuation in the way that was demonstrated in the ITRM CGM substudy and the ITSI study is expected to increase wellbeing, with less symptoms of hyperglycaemia, such as postprandial alertness/ sleepiness, thirst, increased urination or mood changes. However, none of the health outcome measures implemented in the Phase 3 studies showed any difference between treatments; it is clear that these measures were not designed to capture these symptoms. The ambulatory glucose profiles for PPG control at baseline and at Week 26 are very convincing evidence of improved and flattened glucose fluctuation curves in type 1 diabetic patients using LY900014 preprandially in comparison with Humalog and with postprandial administration of LY900014. Preprandial administration increased significantly the time in target glucose and decreased time in hypoglycaemia in type 1 diabetic subjects.

Especially T1D patients are in general insulin sensitive, hence, even small differences in insulin action may have clinical relevance. Eating habits vary from large amounts of fast carbohydrates to people who try to avoid carbohydrates as much as possible. Some patients exercise and cannot wait for several hours after injection before they can exercise again. There are several potential situations, where the

faster-acting bolus insulin would be more practical for the patient. Hence, LY900014 could be a good addition to the insulin treatment armamentarium.

According to the results, LY900014 should optimally be injected just before meal, and not 20 minutes after, as part of the antihyperglycaemic effect is lost when insulin is injected after the postprandial glucose levels have already peaked. Postprandial administration may additionally slightly increase hypoglycaemic events. Nevertheless, the effect of LY900015 taken just after meal resembles that of Humalog taken just before meal. Hence, LY900014 can occasionally be injected also after meal, if necessary.

The overall rate of hypoglycaemic events was similar with both insulins in T1D. However, the different timing of antihyperglycaemic effect of LY900014 and Humalog caused different timing of hypoglycaemia: LY900014 was more prone to increase hypoglycaemia early in postprandial phase and Humalog later on in relation to meal. During the CSII study ITSI, more hypoglycaemic events were observed in the LY900014 than Humalog arm, except for the continuous glucose monitoring results that showed less time in hypoglycaemic range for patients administered LY900014. The CGM results are more comprehensive than SMBG results. It is, however, uncertain if the finding of decreased time in hypoglycaemic range with LY900014 is clinically relevant.

In T2D patients, however, higher documented symptomatic hypoglycaemia rate was observed in the LY900014 group compared to the Humalog group. The long-term clinical relevance of a faster acting insulin is that the patient needs to be aware of the timing of potential hypoglycaemic episodes. Therefore, the information is included in the planned prescribing information, and patients with frequent hypoglycaemic events or hypoglycaemia unawareness are encouraged to discuss this with their treating physician.

The observed difference in the timing of hypoglycaemia did not affect the rate of severe hypoglycaemia or nocturnal hypoglycaemia in either T1D or T2D patients.

The frequency of local reactions at injection and infusion site increased markedly, about 10-fold in patients administered LY900014 vs. Humalog. On the other hand, most reactions were mild to moderate and transient, and only one patient in Phase 3 studies discontinued treatment due to injection site reaction.

3.7.2. Balance of benefits and risks

Non-inferiority of LY900014 in overall glycaemic control (as measured by HbA1c) in comparison with Humalog was demonstrated in both T1D and T2D patients. The PK/PD-profile, efficacy and safety of LY900014 has been well characterised, and the benefit-risk is considered currently to be positive. The achieved improvement in glycaemic control in the postprandial phase is statistically significant in both type 1 and type 2 patients, and has been confirmed by various methods in the clinical trials. The observed improvement in post-meal glucose excursion is more prominent in type 1 diabetic subjects; however, the decrease in glucose peaks is considered clinically relevant also in at least some type 2 diabetic patients. The overall improvement in glycaemia is better defined by continuous glucose monitoring, which has been performed for T1D patients and demonstrates a marked improvement in the incremental AUC of glucose concentration. The Applicant was requested to discuss the observed differences in glycaemic control as regards onset of action and duration of action compared to Humalog: which patients with T1D and T2D are expected to specifically benefit from LY900014 given its faster onset of action compared to the currently approved insulin lispro. The Applicant concluded that the benefit-to-risk is positive in T1D and T2D in general. However, it is expected that patients with uncontrolled post-meal hyperglycaemia with their current treatment would be candidates for LY900014 in clinical practice.

The main target group for this product are T1D patients, who need insulin substitution to cover the missing basal and postprandial insulin secretion. Most T2D patients have multiple other treatment options for postprandial glucose control. As patients needing MDI regimen are a minority among T2D patients, LY900014 obviously is not necessary for most T2D patients. However, there are lean T2D patients who are not very insulin resistant, and the concepts of T1D and T2D are often overlapping. Furthermore, with increasing duration of diabetes, type 2 diabetic patients gradually lose insulin secretion and may need multiple-dose insulin regimens. At that stage, LY900014 may be optimal for some T2D patients, too.

Due to different time-action profile of LY900014 in comparison with Humalog, more hypoglycaemic events within 4 hours from meal are seen in some of the trials. In T2D, the increase in postprandial hypoglycaemia with LY900014 in comparison with Humalog was discussed further by the Applicant. Overall the changes in hypoglycaemic patterns caused by LY900014 are mild to moderate and do not pose the patient in risk more than other treatments with bolus insulins. However, the different timing of maximum effects of LY900014 should be taken in account when a patient is prescribed a faster-acting formulation of bolus insulin, as the change in insulin formulation may affect e.g. need for snacking between meals, timing of exercise, etc. Local irritation at injection or infusion sites occurred in about 2% of patients, which may require the patient to change from one bolus insulin formulation to another in real life. However, only one patient discontinued LY900014 in the Phase 3 studies due to injection site reaction.

The 200 U/ml formulation should not be used in insulin pumps or intravenously, due to a risk of dosing errors and inadvertent overdose.

Dosing of LY900014 should occur prior to meal if feasible, as postprandial glucose control and rate of hypoglycaemia are more beneficial in preprandial vs. postprandial administration. If preprandial dosing is not possible, LY900014 can be injected up to 20 minutes after the meal.

The Applicant stated a wish to keep the name "Liumjev KwikPen Junior" in accordance with the Humalog KwikPen Junior, which also yields insulin in 0.5 unit steps, to avoid confusion in patients switched from Humalog KwikPen Junior to Liumjev KwikPen Junior. Upon request, the Applicant improved the appearance of the carton and pen device, which was initially not considered compatible with marketing authorisation for adults only. It is clearly stated also in the posology of Humalog Junior KwikPen SmPC (as within the Liumjev SmPC), that "it is suitable for patients who may benefit from finer insulin dose adjustments". In other words, Humalog KwikPen junior is also not specifically targeted for pediatric patients, but to all those benefiting from finer dose adjustments. Based on the preliminary data from the ongoing paediatric development of Liumjev, the time-action profile of Liumjev seems even faster in children than adults. It is so far unknown how much and in which way this may affect incidence of hypoglycaemic events in children. The name "Junior" is deemed to carry a risk of off-label use in the paediatric population regardless of the proposed improvements in the carton design. Therefore, the Applicant has confirmed their commitment on the following:

> The potential for medication errors and off-label use in the paediatric population linked to adverse reactions for Liumjev should be monitored, analysed and reported as part of the upcoming PSUSA for insulin lispro (covering all formulations for Humalog, Liprolog and (soon) Liumjev). Based on the analysis of the reported data as part of the upcoming PSUSA, the MAH should also discuss/propose whether further risk minimisation measure(s) are considered necessary at this stage.

The benefit to risk ratio of Liumjev is considered positive.

3.8. Conclusions

The overall B/R of Liumjev is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Liumjev is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Liumjev is favourable in the following indication:

Treatment of diabetes mellitus in adults. The CHMP therefore recommends the granting of the marketing subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

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