13 October 2022
EMA/914290/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Lyumjev

International non-proprietary name: insulin lispro

Procedure No. EMEA/H/C/005037/II/0014

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 antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	assessment report
AST	aspartate aminotransferase
BG	blood glucose
BID	twice daily
BMI	body mass index
B/R	benefit-risk
CFB	change from baseline
CGM	continuous glucose monitoring
CI	confidence interval
CL_{GI}	insulin-dependant glucose clearance
COVID-19	coronavirus disease 2019
CRO	clinical research organization
CSII	continuous subcutaneous insulin infusion
CSR	clinical study report
CV	coefficient of variation
DKA	diabetic ketoacidosis
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
ERB	ethics review board
FGM	flash glucose monitoring
GCP	good clinical practice
HbA1c	haemoglobin A1c
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IP	investigational product
ITSB	I8B-MC-ITSB
ITT	intention-to-treat
IV	intravenous
IWRS	interactive web-response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MDI	multiple-daily-injection
MMRM	mixed-effects model for repeated measures
MMTT	mixed meal tolerance test
MO	major objection
MODD	mean of daily differences
NIM	noninferiority margin
OC	other concern
PD	pharmacodynamic
PedsQL	Paediatric Quality-of-Life
PI	principal investigator
PK	pharmacokinetic
PPG	postprandial glucose
PPK	population pk
PT	preferred term
QD	once daily

RMP	risk management plan
RR	relative rate
RSI	request for supplementary information
SAE	serious adverse event
SAP	statistical analysis plan
SAWP	Scientific Advice Working Party
SC	subcutaneous
SD	standard deviation
SMBG	self-monitored blood glucose
SmPC	summary of product's characteristics
SMQ	Standardised MedDRA Query
SOC	system organ class
T1D	type 1 diabetes
T2D	type 2 diabetes
TE	treatment-emergent
TEADA	treatment-emergent anti-insulin lispro antibodies
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 22 December 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of diabetes mellitus in adolescents and children aged 1 year and above, based on final results from study I8B-MC-ITSB; this is a pivotal Phase 3 study designed to evaluate the safety and efficacy of Lyumjev compared to Humalog in combination with basal insulin in children and adolescent patients with T1D. The study was designed to compare change in HbA1c as the primary endpoint. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement update minor editorial and linguistic changes in the SmPC and Package Leaflet.
As part of the application, the MAH is also requesting one additional year of market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. This request was withdrawn by the MAH during the procedure.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

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: N/A

Timetable	Actual dates
Submission date	22 December 2021
Start of procedure:	23 January 2022
CHMP Rapporteur's preliminary assessment report circulated on:	18 March 2022
PRAC Rapporteur's preliminary assessment report circulated on:	25 March 2022
PRAC members comments	30 March 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022
Updated Rapporteur(s) (Joint) Assessment Report	13 April 2022
Request for supplementary information (RSI)	22 April 2022
MAH's responses submitted to the CHMP on:	18 May 2022
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 June 2022
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	14 July 2022
Request for supplementary information (RSI)	21 July 2022
MAH's responses submitted to the CHMP on:	10 August 2022
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	31 August 2022
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	08 Sept 2022
Request for supplementary information (RSI)	15 Sept 2022
MAH's responses submitted to the CHMP on:	15 Sept 2022
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 Sept 2022
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	n/a
CHMP opinion:	13 October 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The term diabetes describes a group of metabolic disorders characterized and identified by the presence of hyperglycaemia in the absence of treatment. Four diagnostic tests for diabetes are currently recommended, including measurement of fasting plasma glucose; 2-hour (2-h) post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT); HbA1c; and a random blood glucose in the presence of signs and symptoms of diabetes. People with fasting plasma glucose values of ≥7.0 mmol/L (126 mg/dl), 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl) (5), HbA1c ≥ 6.5% (48 mmol/mol); or a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of signs and symptoms are considered to have diabetes (WHO 2019).

The current definition of types of diabetes by the WHO encompasses the following:

- Type 1 diabetes
- Type 2 diabetes
- Hybrid forms of diabetes
    - Slowly evolving immune-mediated diabetes of adults
    - Ketosis prone type 2 diabetes
- Other specific types
    - Monogenic diabetes
        - Monogenic defects of β-cell function
        - Monogenic defects in insulin action
    - Diseases of the exocrine pancreas
    - Endocrine disorders
    - Drug- or chemical-induced
    - Infections
    - Uncommon specific forms of immune-mediated diabetes
    - Other genetic syndromes sometimes associated with diabetes
- Unclassified diabetes
- This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis of diabetes
- Hyperglycaemia first detected during pregnancy
    - Diabetes mellitus in pregnancy
    - Gestational diabetes mellitus

Insulin can be used for treatment of hyperglycaemia regardless of type of diabetes. In children and adolescents, the most frequent type is the auto-immune mediated Type 1 diabetes (T1D). In teenagers, especially of some ethnic groups and associated with obesity, also Type 2 diabetes (T2D) is getting increasingly frequent (see later under subtitle Epidemiology).

The claimed therapeutic indication

Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

Epidemiology

The incidence and prevalence of type 1 diabetes (T1D) are increasing in the world (*Mobasseri et al, Health Promotion Perspectives, 2020, 10(2), 98-115*). Worldwide annual incidence estimate for year 2021 was that around 108,300 children and adolescents under 15 years will be diagnosed in 2021, and this number rises to 149,500 when the age range extends to under 20 years (*Ogle et al. Diabetes Research and Clinical Practice. December 6, 2021*). According to the systematic review by Mobasseri et al, the incidence of type 1 diabetes in Europe was 15 per 100 000 population. However, there is high variation from country to country. The highest incidence (per 100 000 per annum) in children aged 0–14 years is in Finland (52.2) and Sweden (44.1); other European countries appearing within the top 10 of T1D incidence are Norway, the United Kingdom and Ireland (*Ogle et al. Diabetes Research and Clinical Practice. December 6, 2021).* The peak age of onset of T1D varies substantially. In Finland, T1D incidence peaks in the 5–9 years age group and in most non-European origin populations in the 10–14 years group (*Ogle et al. Diabetes Research and Clinical Practice. December 6, 2021).*

Until recently, type 2 diabetes (T2D) was seen mainly in middle-aged and elderly people. However, T2D is now occurring increasingly frequently in children and adolescents as well. One reason is increasing prevalence of obesity. However, even though obesity is often observed in children and adolescents with T2D from Western regions, such as the USA and Europe, up to 30–50 % of youth-onset T2D cases in Eastern countries, such as Japan, India, and Taiwan, have normal weight. Overall, available country-specific epidemiology data for youth-onset T2D are varied and scant. Incidence is especially high in some ethnic minorities such as African American, Aboriginal, Hispanic, Asian, and Pacific Island descendants, compared with non-Hispanic White. (*Lynch et al. Country-Specific Prevalence and Incidence of Youth-Onset Type 2 Diabetes: A Narrative Literature Review Ann Nutr Metab 2020;76:289–296*)

Management

Rapid-acting insulins are used as subcutaneous (sc.) injections given prior to or at mealtime to prevent postprandial glucose excursions or as continuous subcutaneous insulin infusion (CSII) via insulin pump to provide both basal and mealtime insulin to the patient.

The major difference of LY900014 (faster-acting lispro insulin) in comparison with Humalog (lispro insulin) is the time-action profile, which is shifted to the left in adult studies; hence, the glucodynamic effect starts earlier and ends earlier and as such resembles more closely the physiological postprandial insulin excursions in healthy subjects. In adults with T1D, a marked reduction in postprandial glycaemia, as compared with Humalog, was seen when both were injected prior to meal. In adult T2D subjects, the corresponding reduction in postprandial 2-hour glucose was less marked than in T1D. In clinical practice, it is expected that patients chosen to use LY900014 would be the individuals with uncontrolled post-meal glucose excursions.

In adult subjects, the effect of LY900014 taken just after meal resembled that of Humalog taken just before meal. Hence, LY900014 can occasionally be injected also after meal, if necessary. This option would be important in the paediatric population as well, especially toddlers, for whom it may not be possible to anticipate the amount of ingested carbohydrates prior to meal. In such instances, it is practical if mealtime insulin dose can be decided after the meal.

2.1.2. About the product

Lyumjev (LY900014) is a rapid-acting (fast-acting) formulation of insulin lispro. LY900014 is approved for the treatment of diabetes mellitus in adults in the EU.

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

The LY900014 formulation includes 2 enabling excipients, treprostinil and citrate, with independent mechanisms to accelerate the absorption of insulin lispro from the site of injection or infusion. These mechanisms result in rapid absorption that leads to greater early glucose lowering postmeal and earlier offset of insulin action compared to Humalog. These 2 mechanisms include

- 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
- accelerated absorption of insulin through enhanced local vascular permeability, which is achieved by addition of the excipient sodium citrate in the formulation.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice

In the EMA scientific advice in 2016 (EMA/CHMP/SAWP/400498/2016) the MAH inquired if it would be sufficient to request a similar indication to the current Humalog licence, including children and adolescents, in case the pharmacokinetic (PK) profile of insulin lispro after administration of LY900014 in paediatric patients is similar to that already observed in adult patients. The CHMP responded that clinically relevant advantage of LY900014 over insulin lispro in adults does not necessarily mean the same benefit for children using smaller volumes, with relatively larger surface areas of subcutaneous doses and thus a potentially different additive effect of treprostinil, and differences in fat mass and subcutaneous fat in small children compared to adults. Therefore, PK studies alone were not considered adequate for MA in children, hence, data from a clinical efficacy and safety study was considered necessary. This advice has been followed by the MAH.

2.1.4. General comments on compliance with GLP, GCP

GLP

Not applicable

GCP

The MAH confirms that clinical trials that support this use of Lyumjev were conducted in accordance with:

1) Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects

2) The International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6]

3) Applicable laws and regulations of the country or countries where a study is conducted

Clinical trials conducted outside the European Union meet the ethical requirements of Directive 2001/20/EC and are listed below:

Study I8B-MC-ITSB: United States, Russia, Czech Republic, Ukraine, Brazil, Israel, United Kingdom, Mexico, China, and Japan

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Environmental risk assessment was included for this Type II variation including extension of indication in according to the current ERA guideline (CPMP/SWP/4447/00 corr2).

The Phase I environmental risk assessment (ERA) focusing on excipient treprostinil submitted with the original MAA for LY900014 for adult indication, was provided.

In LY900014, the amount of treprostinil in the drug product is 10 ng/U. A maximum high dose of insulin for type 2 diabetic patients is 3 units/kg/day. Assuming that all insulin used is LY900014 and a body weight of 100 kg, the maximum daily dose of treprostinil is 3000 ng, or 0.003 mg. The calculated $PEC_{surface\ water}$ for treprostinil was 0.000015 µg/L, and lower than the action limit of 0.01 µg/L. Therefore, is unlikely to be a risk for the environment following patient use.

The sum of predicted environmental concentrations of treprostinil from use as an excipient in LY900014 and for treatment of PAH is 0.000022 µg/L. Since the expected concentration of treprostinil is less than 0.01 µg/L, it is unlikely that it will be a risk to the environment. Neither insulin lispro nor treprostinil should be classified as persistent, bioaccumulative and toxic.

2.2.2. Discussion on non-clinical aspects

No new nonclinical data was submitted in this type II variation. This is in general acceptable but considering that LY900014 includes excipient treprostinil (a prostacyclin analogue), justification for its safe use in proposed paediatric patients was asked.

There are limited data on the use of treprostinil in paediatric patients. Paediatric assessments have not been required for treprostinil because of its orphan drug designation; thus, the safety and effectiveness of treprostinil in paediatric patients have not been established. SC treprostinil has been evaluated in children with PAH in an observational study (n = 8). Patients initially received a fixed treprostinil dose of 1.25 ng/kg/minute, which was gradually increased according to general and local tolerance, reaching a median of 40 ng/kg/min (range, 37 to 60 ng/kg/min) over the duration of follow-up (6- to 18-month time period) after initiation of treprostinil therapy. Six children had symptomatic and haemodynamic response to the addition of SC treprostinil, with manageable control of local injection-site discomfort (Levy et al. 2011).

The amount of treprostinil will vary based upon the LY900014 dose administered (10 ng/U of treprostinil in LY900014), and treprostinil exposure has not been detected in adults at doses up to 50 U LY900014 following MDI studies or up to 18 U bolus dose with a basal infusion (up to 16 ng/hour) with CSII therapy.

On average, the paediatric population will use a lower preprandial insulin dose, further lowering exposure to treprostinil in this population.

The MAH provided a justification based on lack of toxicity of treprostinil in nonclinical studies, negligible systemic exposure in patients, and the general clinical safety profile of LY900014 for safe use treprostinil as excipient in paediatric patients.

Assessment of paediatric data on non-clinical aspects

The safety of insulin containing medicinal products is well characterised in paediatric patients. Regarding the treprostinil excipient, the MAH did not initially include any discussion to justify the safe use of this excipient in paediatric patients in their extension of indication application, and further justification was requested and further provided by the MAH.

In preclinical safety pharmacology and toxicity studies, or clinical pharmacology studies involving LY900014 or treprostinil alone, other than known risks associated with Humalog and Remodulin, no additional risks were identified. Repeat SC dosing with treprostinil sodium for up to 26 weeks was well tolerated in rats and dogs. Local and systemic toxicity profiles of Humalog and Remodulin do not suggest the potential for additive or synergistic toxicity. During Lyumjev original MAA submission, no juvenile animal toxicity studies were done, but reproduction and development toxicity studies were conducted. Studies in juvenile animals were not deemed necessary based on the weight-of-evidence risk assessment to support the use of LY900014 containing treprostinil in paediatric patients in line with the ICH S11. This approach was agreed also by CHMP (advice procedure on 2017).

In reproduction and developmental toxicity studies in rats, no treprostinil-related effects were noted up to 0.1 mg/kg/day, corresponding to a safety margin of 415-fold in comparison to the clinically relevant exposure (AUC) of treprostinil received via LY900014.

No evidence of harm to the foetus or growth and development of the offspring was noted in reproductive and developmental toxicity studies of treprostinil to support the marketing authorisation of Remodulin (Remodulin SmPC 2014) at allometric dose multiples 140-fold the maximum daily dose of treprostinil in LY900014 (that is, 15 ng/kg/day).

2.2.3. Conclusion on the non-clinical aspects

No new nonclinical data was submitted for variation II for the extension indication to paediatrics. The safety of insulin-medicinal products is well characterised in paediatric patients. LY900014 includes treprostinil excipient. There are limited data on the use of treprostinil in paediatric patients, but the MAH provided adequate justification for the safe use of Lyumjev containing treprostinil for the treatment of diabetes mellitus in paediatric patients. The extrapolated total daily treprostinil exposure AUC(0-24h) for 3 pre-prandial doses of LY900014 containing 50 U of insulin lispro (500 ng of treprostinil) is estimated to be 1000-fold lower than that following SC therapeutic dosing of Remodulin in adult indications. The amount of treprostinil will vary based upon the LY900014 dose administered (10 ng/U of treprostinil in LY900014), but on average, the paediatric population will use a lower preprandial insulin dose, further lowering exposure to treprostinil.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of insulin lispro (containing treprostinil). Considering the above data, insulin lispro (containing treprostinil) is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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.

- **Tabular overview of clinical studies**

All LY900014 studies in paediatric patients are listed in Table 1.

The submission package includes the following clinical studies in which LY900014 was administered to paediatric patients with T1D:

- One Phase 3 study, Study ITSB, provides data to support the inclusion of the paediatric patient population to the EU Summary of Product Characteristics (SmPC) for LY900014. This is a pivotal Phase 3 study designed to evaluate the safety and efficacy of Lyumjev compared to Humalog in combination with basal insulin in children and adolescent patients with T1D. The study was designed to compare change in HbA1c as the primary endpoint.
- One clinical pharmacology study, Study ITSA, characterized the PK and PD during a test meal of LY900014 and Humalog following a single SC bolus dose administered through injection (study Part A) or CSII (study Part B) in paediatric and adult patients with T1D. Study ITSA was previously assessed in Article 46 procedure EMEA/H/C/005037/II/0005. Main results of study ITSA are summarized in sections 2.3.2 and 2.3.3 of this assessment report (AR).

The evaluation of clinical efficacy and safety of LY900014 in children and adolescents aged from 1 year to <18 years is in this procedure based on Study ITSB and assessed in Sections 2.4 to 2.5 of this AR.

In addition, the MAH has submitted several population PK and PK/PD modelling and simulation analyses, which are assessed and discussed in Sections 2.3.4 and 2.3.5 of this AR.

Table 1 Completed LY900014 Studies in Paediatric Patients

Study Identifier; Location of Report; Type of Report; Study Status	Healthy Subjects or Diagnosis of Patients	Study Design	Duration of Treatment	Treatment Groups, Regimens, and Routes of Administration	Key Objective	Number of Subjects
I8B-MC-ITSA US: 5.3.4.2 EU: 5.3.4.2 Clinical Pharmacology Study Report Completed	Patients with T1D **Age**: Children: 6 to <12 years Adolescents: 12 to <18 years Adults: 18 to <65 years	Multicenter, Phase 1, randomized, 2-part, patient- and investigator-blind, 2-period, crossover study in children, adolescents, and adults with T1D currently using a CSII pump or an MDI regimen **Part A:** Patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus injection **Part B**: Patients received a single dose of LY900014 and Humalog on 1 occasion each as SC bolus via CSII	**Screening:** up to 28 days **Treatment period:** 2 inpatient days, across 2 study periods Each study period was separated by at least and no more than 22 days **Follow-up:** ≥14 days after last dose	**Treatment:** Test: 100 U/mL LY900014 (final commercial formulation) Reference: 100 U/mL Humalog **Route of administration:** SC or CSII	**Part A:** To evaluate the PK of insulin lispro following a single SC dose administered through injection of LY900014 compared to Humalog in children, adolescents, and adults with T1D.	**Part A:** Planned: 45 Randomized: 42 Treated (at least 1 dose): 42 Completed: 41
					Part B: To evaluate the PK of insulin lispro following a single SC bolus dose administered through CSII of LY900014 compared to Humalog in children, adolescents, and adults with T1D.	**Part B:** Planned: 45 Randomized: 39 Treated (at least 1 dose): 37 Completed: 37
I8B-MC-ITSB 5.3.5.1 Clinical study report for 26-week primary endpoint CSR Addendum: Continuous Glucose Monitoring Completed	Patients with T1D **Age**: adolescents: 1 to <18 years	Phase 3, prospective, randomized, outpatient, multinational, multicenter, parallel, active-controlled study conducted in children and adolescent patients with T1D currently using an MDI regimen	**Screening:** up to 1 week **Lead-in:** 4 weeks **Treatment period:** 26 weeks **Safety follow-up:** 2 weeks	**2 Double-blind arms:** Test: 100 U/mL LY900014 (final commercial formulation) Reference: 100 U/mL Humalog Timing: administered 0 to 2 minutes prior to each meal **Open-label arm:** LY900014 (final commercial formulation) Timing: up to 20 minutes after the start of a meal **Route of administration:** SC	To test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (using an NIM of 0.4% and 0.3% for HbA1c) in children and adolescents with T1D when administered as prandial insulin (0 to 2 minutes prior to the meal) in combination with basal insulin as part of an MDI regimen for 26 weeks.	**Planned**: 708 **Randomized**: 716 Double-blind arm: LY900014: 280 Humalog: 298 Open-label arm: 138 **Treated (received at least 1 dose of randomly assigned IP):** 716 Double-blind arm: LY900014: 280 Humalog: 298 Open-label arm: 138 **Completed study**: 689 Double-blind groups: LY900014: 266 Humalog: 288 Open-label arm: 135

Abbreviations: CSII = continuous subcutaneous insulin infusion; CSR = clinical study report; IP = investigational product; MDI = multiple-daily-injection; NIM = noninferiority margin; PK = pharmacokinetics; SC = subcutaneous; T1D = type 1 diabetes.

2.3.2. Pharmacokinetics

Analytical methods

Quantification of insulin lispro in human serum samples

Human serum samples obtained during these studies were analyzed for free insulin lispro using a validated enzyme-linked immunosorbent assay method at Charles River Laboratories Montreal located in Senneville, Quebec, Canada. The assay is specific for insulin lispro and endogenous insulin does not cross-react in the assay. The method has been a part of the original MAA.

Detection of anti-insulin lispro antibodies in human serum

In the clinical studies of LY900014 included in this submission, a radioligand binding assay (RBA) was used for the detection of anti-insulin lispro antibodies in human serum. In Study ITSB, the same RBA was implemented by 2 vendors: one intended for samples collected in the People's Republic of China (PRC) at WuXi AppTec (WaiGaoQiao Free Trade Zone, Shanghai, China), and the other intended for samples collected from patients outside the PRC at Eurofins (Saint Charles, MO, USA). Results of the assay validation at WuXi, including validation parameters and relevant validation reports, are described. Results of the assay validation at Eurofins are described in the original MAA submission.

In the RBA a radiolabeled insulin tracer is incubated with sample overnight in assay buffer. After an overnight incubation, bound anti-insulin antibodies are precipitated with bovine gamma globulin and PEG, centrifuged and the supernatant removed. The pellet that forms is then washed with PEG and centrifuged. The supernatant is removed, and the pellet is counted on a gamma counter.

The validation at WuXi AppTec included the following parameters: Confirmation of MRD, Anti-insulin lispro assay cut point and specificity (Tier 1), Cross-reactivity to insulin assay cut point and specificity (Tier 2), Anti-insulin lispro sensitivity, Cross-reactivity to insulin sensitivity, Drug tolerance to LY275585, Insulin tolerance, Intra- and inter-assay precision, Assay robustness (Minimum and maximum incubation times were tested) and Minimum significant ratio (MSR).

Table 2 provides a side-by-side comparison of critical assay parameters from the 2 clinical research organizations. Validations for this assay showed concordance in sensitivity, drug tolerance, and precision.

Table 2. Comparison of Key Validation Parameters

Validation Parameter	WuXi	Eurofins
Tier 1 Sensitivity (Anti-Insulin Lispro Assay)	10.24 ng/mL ADA[a]	17.1 ng/mL ADA[a]
Tier 2 Sensitivity (Cross-Reactivity to Insulin Assay)	13.83 ng/mL ADA[a]	10.9 ng/mL ADA[a]
Insulin Lispro tolerance at 100 ng/mL ADA	0.6934 µg/mL LY900014	0.3647 µg/mL LY900014
Native insulin tolerance at 100 ng/mL ADA	0.8151 µg/mL native insulin	0.4722 µg/mL native insulin
Inter-assay precision	8.37% to 14.19% CV	8.8% to 13.6% CV

[a] Serum from hyperimmunized guinea pigs was affinity purified against LY900014 and used as ADA positive control material.

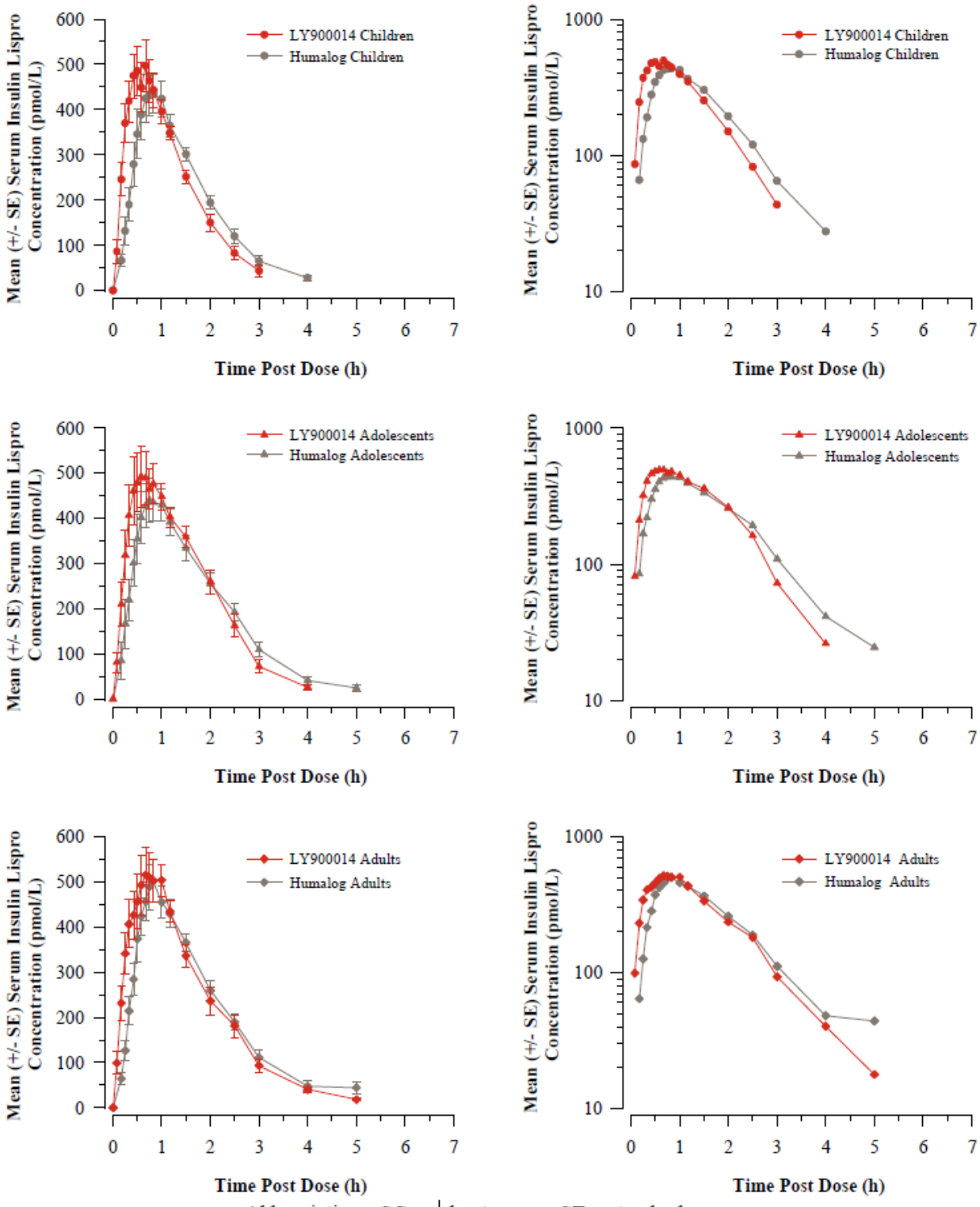
Study ITSA

Study ITSA was a randomised, 2-part, patient- and investigator-blind, 2-period crossover study in children, adolescents, and adults with T1D. The primary objective of the study was to evaluate the PK of insulin lispro following a single SC bolus dose administered through injection (study Part A) and CSII (study Part B) of LY900014 compared to Humalog in children, adolescents, and adults.

In ITSA Part A, patients received a single 0.2 U/kg dose of either LY900014 or Humalog on each period as SC bolus injection immediately prior to a standardised liquid mixed meal. The primary PK endpoints were time to early half-maximal drug concentration [early 50% tmax] and AUC(0-30min). Of the 42 patients randomised, 13 were children aged 8 to 11 years, 14 were adolescents aged 12 to 16 years, and 15 were adults aged 18 to 58 years. One adult patient discontinued from the study.

LY900014 showed an accelerated insulin lispro absorption with a reduction in late insulin exposure compared to Humalog across all 3 age groups (Figure 1 and Table 3).

Figure 1. Study ITSA Part A: Mean insulin lispro concentration (± SE) versus time following a 0.2 U/kg SC bolus injection of LY900014 or Humalog in children (top), adolescents (middle) and adults (bottom) with T1D. Shown in linear scale (left panel) and log scale (right panel).



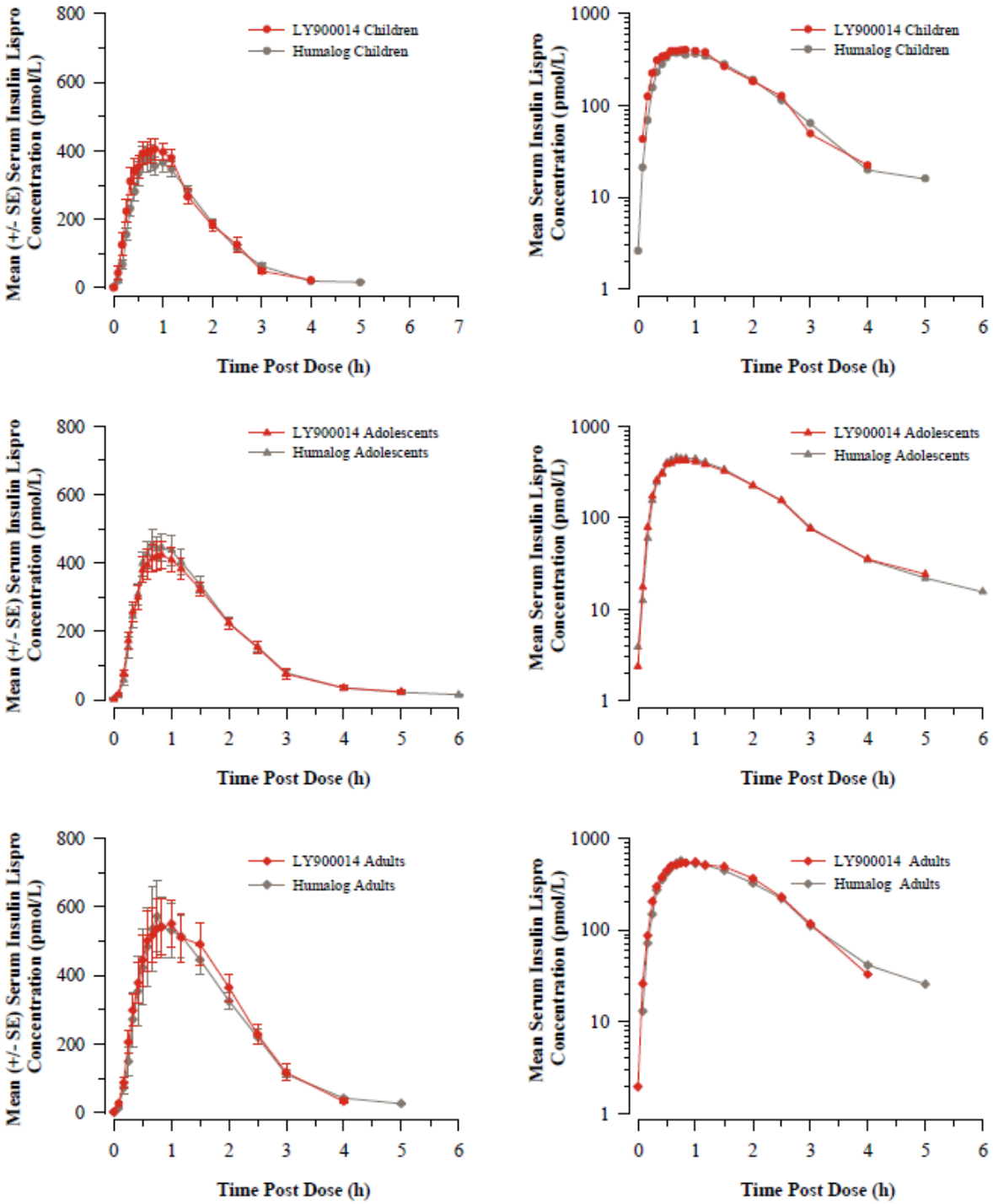
Abbreviations: SC = subcutaneous; SE = standard error.

In ITSA Part B, patients received a single 0.2 U/kg dose of either LY900014 or Humalog on each study period as SC bolus infusion via CSII (single wave bolus with a standard delivery speed of 1.5 U/minute)

immediately prior to a standardised liquid mixed meal. The catheter was inserted the night before with low continuous delivery overnight. Of the 39 patients randomised, 12 were children aged 8 to 11 years, 13 were adolescents aged 12 to 17 years, and 14 were adults aged 18 to 58 years. Two adult patients withdrew from the study.

The mean insulin lispro exposures in children, adolescents, and adults are shown in Figure 2. Numerical results for the two primary PK parameters [early 50% tmax and AUC(0-30min)] and selected secondary PK parameters are summarized in Table 3. No statistically significant differences between LY900014 and Humalog were observed for the PK parameters [early 50% tmax and AUC(0-30min)], Cmax and tmax. The insulin lispro exposure within the first 15 minutes [AUC(0-15min)] was increased by 1.61-fold in children (p=0.0397), by 1.38-fold in adolescents (p=0.1266), and 1.66-fold in adults (p=0.0229) after LY900014 administration compared to Humalog.

Figure 2. Study ITSA Part B: Mean insulin lispro concentration (± SE) versus time following a 0.2 U/kg SC bolus infusion of LY900014 or Humalog in children (top), adolescents (middle) and adults (bottom) with T1D. Shown in linear scale (left panel) and log scale (right panel).



Abbreviations: SC = subcutaneous; SE = standard error.

Predose anti-insulin lispro antibodies (ADA) were very common in patients in study ITSA. In Part A, predose ADA were detected in all patients except 1 adolescent and 3 adults. In Part B, predose ADA were detected in all patients except 2 adults.

Pharmacokinetics across adult and paediatric studies: SC injection

The PK profiles between LY900014 and Humalog following a single SC injection in children (Study ITSA: Part A), adolescents (Study ITSA: Part A), and adults with T1D (Studies ITRR, ITRV, and ITSA: Part A) were compared by the MAH. This analysis was possible as these studies used the final commercial formulation of LY900014, included Humalog as the comparator, collected PK data in a crossover study design, used similar timing for PK collection, and conducted comparisons between LY900014 and Humalog using the same dose level. Patient demographics are summarized in Table 4.

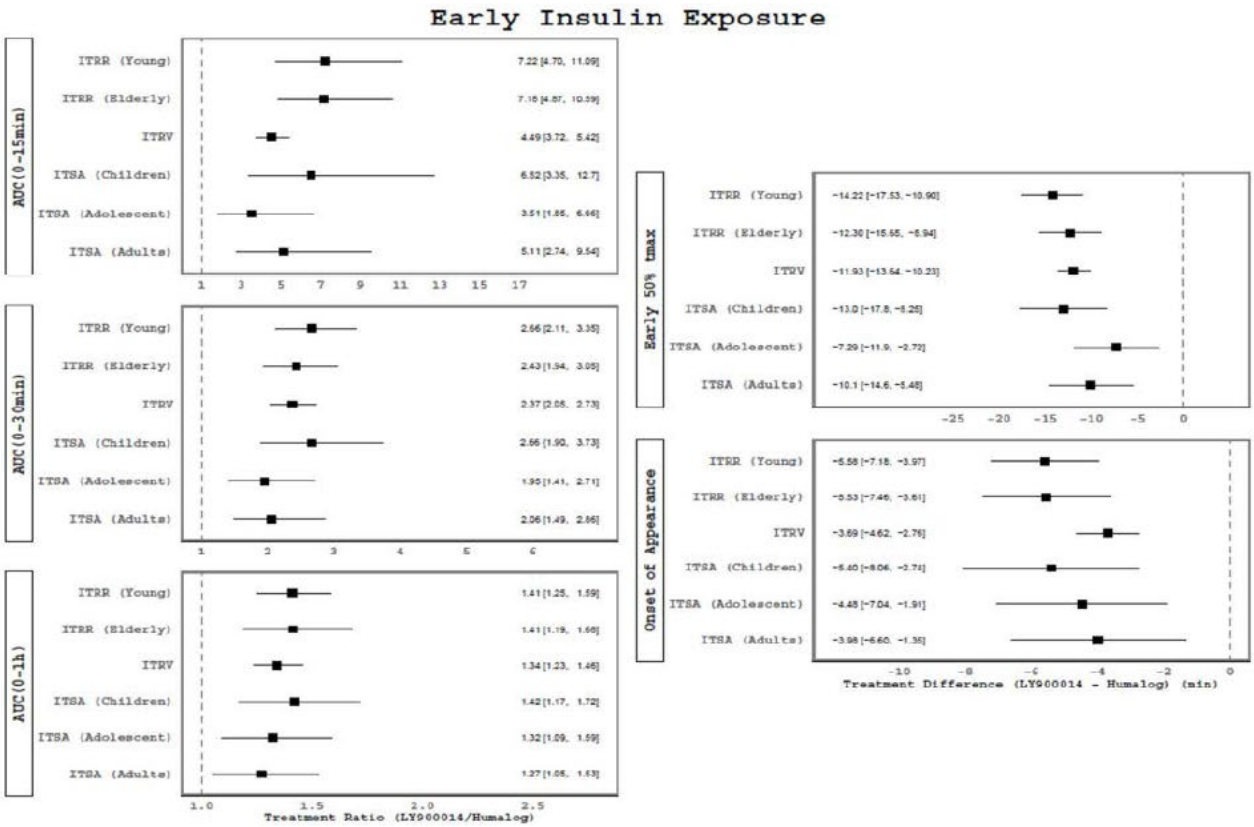
Table 4. Demographics for studies conducted in patients with T1D on SC injection therapy

	Children (Study ITSA: Part A)	Adolescents (Study ITSA: Part A)	Adults (Study ITSA: Part A)	Younger Adults (Study ITRR)	Elderly Adults (Study ITRR)	Adults (Study ITRV)
Number of subjects	13	14	15	41	39	36
Age (years)	9.5 (1.0)	14.1 (1.5)	36.0 (15.9)	32.0 (6.8%)	68.5 (2.7)	45.4 (11.3)
Male, n (%)	4 (30.8)	9 (64.3)	9 (60.0)	28 (68.3)	22 (56.4)	27 (75.0)
Female, n (%)	9 (69.2)	5 (35.7)	6 (40.0)	13 (31.7)	17 (43.6)	9 (25.0)
Hip circumference (cm)	NA	NA	92.49 (7.70)	99.28 (6.65)	101.39 (6.92)	98.44 (10.08)
Waist circumference (cm)	NA	NA	83.21 (10.30)	89.43 (9.14)	95.06 (11.34)	92.90 (8.62)
Body weight (kg)	34.76 (6.08)	62.55 (11.43)	75.52 (10.25)	78.39 (10.00)	76.66 (12.81)	80.56 (12.56)
BMI (kg/m^2)	17.30 (1.26)	21.21 (2.40)	24.05 (2.39)	24.77 (2.35)	26.23 (2.63)	25.39 (2.80)
Duration of T1D (years)	5.3 (2.6)	6.9 (4.4)	17.5 (10.9)	17.670 (9.262)	37.493 (14.657)	21.41 (13.60)
HbA1c (%)	7.75 (0.89)	7.69 (1.07)	7.70 (1.03)	7.19 (0.60)	7.21 (0.71)	7.26 (0.72)

Abbreviations: BMI = body mass index; HbA1c = glycosylated hemoglobin; MDI = multiple daily injections; NA = not applicable; SD = standard deviation; T1D = type 1 diabetes.
Values are presented as Mean (SD).
Source: ITSA CSR Table ITSA.6.1, ITRR CSR Table ITRR.6.1, ITRV CSR Table ITRV.6.1.

A consistent, faster insulin absorption was observed with LY900014 compared to Humalog across these parameters in children, adolescents, and adults across these clinical pharmacology studies (Figure 3). Furthermore, LY900014 reduced the late insulin lispro exposure compared to Humalog for all study populations, and the total insulin lispro exposure (AUC[0-inf]) and tmax were comparable between LY900014 and Humalog in children, adolescents, and adults.

Figure 3. Mean treatment difference or ratio (LY900014 vs Humalog) and 95% CIs for the early insulin lispro PK parameters in children, adolescents, and adults with T1D.



AUC(0-X) = AUC from time 0 to X postdose; **early 50% tmax** = time to early half-maximal concentration; **onset of appearance** = time from study drug administration until the first time serum insulin lispro concentrations reached above the lower limit of quantification

Pharmacokinetics across adult and paediatric studies: CSII

The PK profiles between LY900014 and Humalog in children (Study ITSA: Part B), adolescents (Study ITSA: Part B), and adults with T1D (Studies ITSA: Part B, ITSC, and ITRF) during CSII therapy were compared using the early, late, and total PK parameters. This analysis was achievable, as these studies included Humalog as the comparator, collected PK data in a crossover study design, used similar timing for PK collection, and conducted comparisons between LY900014 and Humalog using the same dose (bolus dose and basal rate) in some parts of the studies.

Table 5 shows the comparison of the patient demographics between children, adolescents, and adults with T1D in studies conducted with CSII therapy. The adults in Study ITSA were similar to the adults in both Studies ITRF and ITSC. Accelerated insulin lispro absorption for was previously demonstrated with LY900014 compared to Humalog in adults (Studies ITSC and ITRF), and numerically similar results were observed in children and adolescents in study ITSA Part B (Table 6). Overall, pharmacokinetic differences between LY900014 and Humalog appeared to be lesser following CSII bolus infusion compared with differences observed following SC injection.

Table 5. Demographics for studies conducted in patients with T1D on CSII therapy

	Children (Study ITSA) (Part B)	Adolescents (Study ITSA) (Part B)	Adults (Study ITSA) (Part B)	Adults (Study ITSC)	Adults (Study ITRF)
Number of subjects	12	13	14	24	30
Age (years)	9.4 (0.9)	14.5 (1.6)	31.3 (12.4)	48.6 (11.4%)	42.6 (12.8)
Male, n (%)	2 (16.7)	10 (76.9)	6 (42.9)	18 (75.0)	17 (56.7)
Female, n (%)	10 (83.3)	3 (23.1)	8 (57.1)	6 (25.0)	13 (43.3)
Body weight (kg)	37.45 (4.95)	66.78 (8.99)	71.01 (12.07)	83.70 (12.11)	78.97 (9.66)
BMI (kg/m^2)	17.72 (1.52)	21.59 (2.16)	23.68 (2.70)	26.88 (2.49)	25.45 (2.72)
Duration of T1D (years)	5.8 (2.2)	8.1 (4.7)	18.6 (7.1)	28.8 (12.4)	24.1 (12.2)
HbA1c (%)	7.44 (0.90)	8.36 (1.09)	7.72 (0.91)	7.04 (0.79)	7.44 (0.87)

Abbreviations: BMI = body mass index; CSII = continuous subcutaneous insulin infusion; HbA1c = glycosylated hemoglobin; SD = standard deviation; T1D = type 1 diabetes.

Values are presented as Mean (SD).

Source: ITSA CSR Table ITSA.6.2., ITRF CSR Table ITRF.6.1., ITSC CSR Table ITSC.6.1.

Table 6. Mean Treatment Difference or Ratio and 95% CIs between LY900014 and Humalog for the Insulin Lispro PK Parameters of Early, Late, and Total Exposure in Studies ITSA, ITSC, and ITRF

		Mean Treatment Difference (LY900014 - Humalog) or Ratio (LY900014:Humalog) (95% CI)				
PK Parameters		**Children (Study ITSA)**	**Adolescents (Study ITSA)**	**Adults (Study ITSA)**	**Adults (Study ITSC) Day 1**	**Adults (Study ITRF) Day 1**
	Early Insulin Lispro Exposure					
Early 50% t_{max} (min)	Difference	-1.65 (-6.46, 3.15)	-1.01 (-5.52, 3.50)	-2.75 (-7.37, 1.87)	-8.58 (-11.1, -6.06)	-3.75 (-4.91, -1.66)
$AUC_{(0\text{-}15min)}$ (pmol·h/L)	Ratio	1.61 (1.02, 2.53)	1.38 (0.91, 2.09)	1.66 (1.08, 2.57)	1.58 (1.25, 1.98)	1.49 (1.28, 1.75)
$AUC_{(0\text{-}30min)}$ (pmol·h/L)	Ratio	1.28 (0.90, 1.81)	1.02 (0.74, 1.41)	1.34 (0.96, 1.88)	1.46 (1.14, 1.86)	1.31 (1.14, 1.52)
$AUC_{(0\text{-}1h)}$ (pmol·h/L)	Ratio	1.14 (0.91, 1.44)	0.95 (0.77, 1.17)	1.11 (0.89, 1.38)	1.17 (0.93, 1.48)	1.20 (1.05, 1.38)
	Late Insulin Lispro Exposure					
Duration (min)	Difference	-30.0 (-58.7, -1.36)	-66.9 (-103, -30.5)	-45.3 (-75.4, -15.3)	NC	NC
Late 50% t_{max} (min)	Difference	-7.09 (-29.2, 15.1)	8.28 (-12.1, 28.7)	1.66 (-19.6, 22.9)	-12.2 (-33.9, 9.49)	NC
$AUC_{(2\text{-}Xh)}$ (pmol·h/L)	Ratio	0.93 (0.76, 1.13)	0.94 (0.78, 1.13)	0.88 (0.73, 1.07)	NC	NC
$AUC_{(3\text{-}Xh)}$ (pmol·h/L)	Ratio	0.869 (0.63, 1.20)	0.86 (0.64, 1.16)	0.70 (0.52, 0.96)	NC	NC
	Total Insulin Lispro Exposure					
C_{max} (pmol/L)	Ratio	1.12 (0.94, 1.34)	0.91 (0.77, 1.07)	1.03 (0.87, 1.23)	0.99 (0.78, 1.25)	1.14 (0.987, 1.32)
t_{max} (min)	Difference	3.75 (-8.34, 15.8)	7.44 (-3.66, 18.6)	1.78 (-9.84, 13.4)	-6.24 (-18.6, 6.12)	NC
$AUC_{(0\text{-}inf)}$ (pmol·h/L)	Ratio	1.04 (0.96, 1.13)	0.97 (0.90, 1.05)	1.02 (0.94, 1.10)	0.99 (0.80, 1.23)	1.08 (0.92, 1.26)[a]

AUC(0-inf) = AUC from time zero to infinity; AUC(0-15min) = AUC from time zero to 15 minutes postdose; AUC(0-30min) = AUC from time zero to 30 minutes postdose; AUC(0-1h) = AUC from time zero to 1 hour postdose; AUC(2-Xh) = AUC from time 2 to X hours postdose; AUC(3-Xh) = AUC from time 3 to X hours postdose; Cmax = maximum observed drug concentration; NC = not calculated; tmax = time to maximum observed drug concentration. X is the end of the PK sampling period, which was up to 7 hours after infusion in Studies ITSA and up to 5 hours after infusion in Studies ITRF and ITSC.
a Change from baseline AUC(0-inf).

2.3.3. Pharmacodynamics

Study ITSA

Evaluation of the differences in postprandial glucodynamic response to LY900014 and Humalog administered through SC bolus injection or CSII was a secondary objective of study ITSA Parts A and B. Patients were provided standardised liquid meals for the mixed meal tolerance test (MMTT). For adults, the meal consisted of 2 cans of 8 fl/oz (total of 474 mL) Abbott Ensure Plus® (approximately 100 g of carbohydrates total). For children and adolescents, the volume (and carbohydrate content) of the meal was adjusted based on the patient's body weight. The test meal was to be completed within 15 minutes of starting the meal and the patients were expected to not consume any further food until the completion of blood glucose collection (approximately 300 minutes). The study drug (LY900014 or Humalog) was administered immediately before the start of the test meal in study Parts A and B. The primary PD endpoints

were change from baseline glucose area under concentration versus time curve from time 0 to 2 hours and from 0 to 5 hours postmeal [BGΔAUC(0-2h) and BGΔAUC(0-5h), respectively].

In study Part A, a total of 6 patients had hypoglycaemic or hyperglycaemic event(s) and received intervention during the MMTT. Figure 4 presents the mean glucose excursions over time after SC injection of LY900014 and Humalog by age group. Statistical analysis for key glucodynamic parameters, excluding data after any treatment intervention, are summarised in Table 7.

Figure 4. ITSA Part A: Mean glucose excursions (± SE) vs. time following liquid mixed meal with a 0.2 U/kg SC dose of LY900014 or Humalog in children (upper), adolescents (middle) and adults (lower) with T1D.

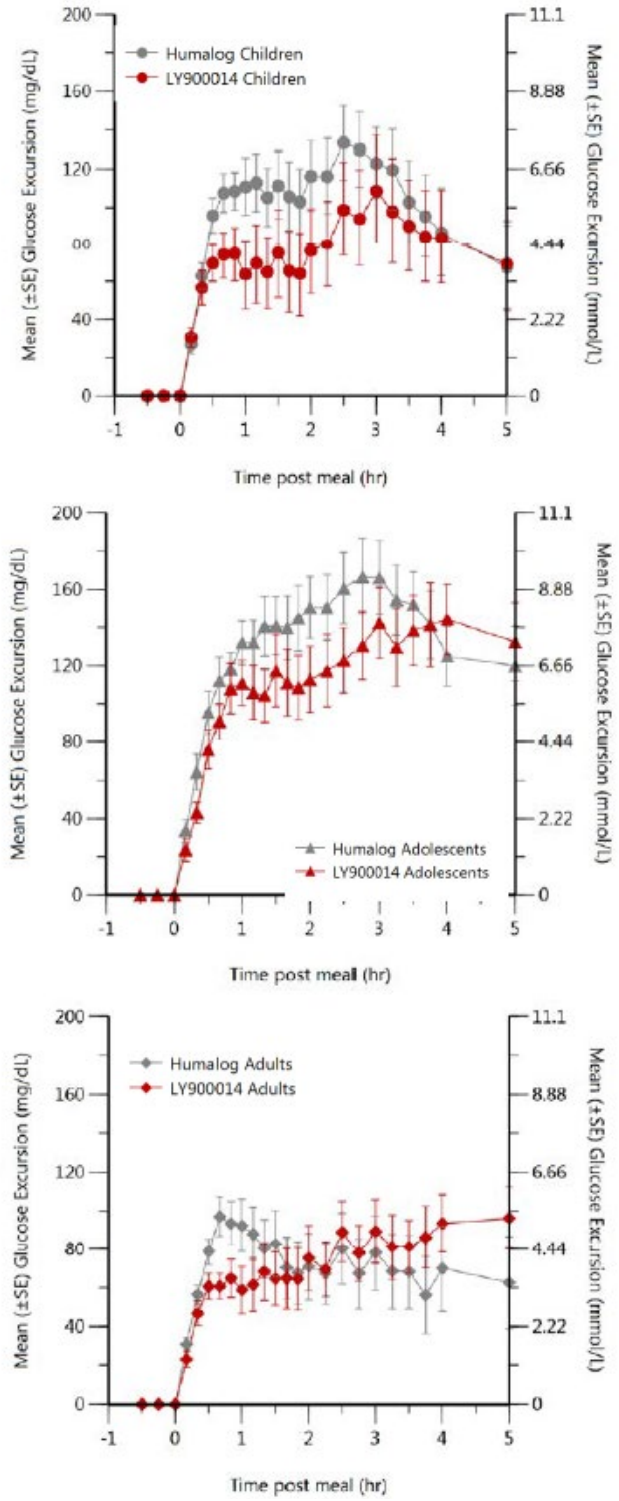


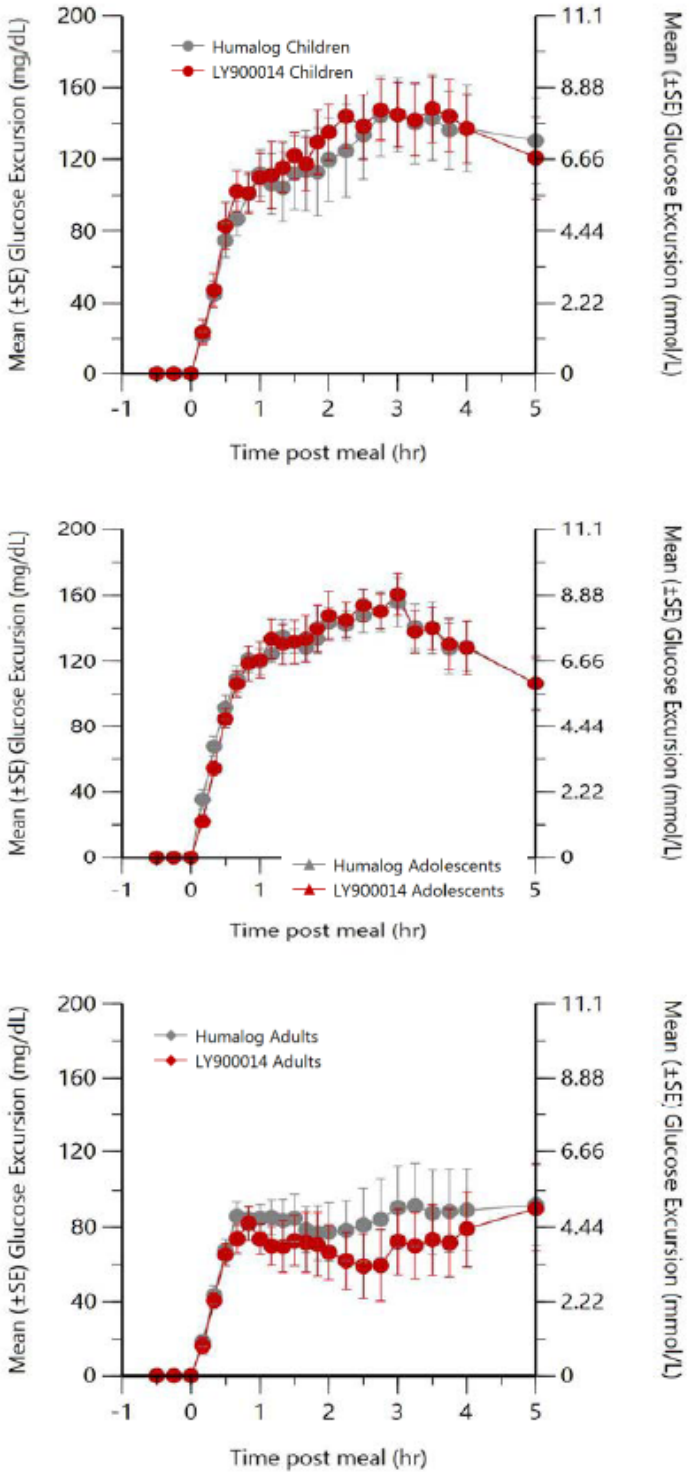
Table 7. Study ITSA Part A: Statistical analysis of primary glucodynamic parameters (excluding data after any treatment intervention)

Parameter	Treatment	N	LSM	Difference in LSM (LY900014 - Humalog)	95% CI for the difference	P-value	Ratio of LSM (LY900014: Humalog)	95% CI for the ratio
Children								
BGΔAUC(0-2h) (mg·h/dL)	Humalog LY900014	12 12	180.69 130.06	-50.63	(-95.06, -6.20)	0.0267	0.72	(0.46, 0.99)
BGΔAUC(0-5h) (mg·h/dL)	Humalog LY900014	10 10	421.03 481.36	60.32	(-69.64, 190.29)	0.3522	1.14	(0.84, 1.59)
Adolescents								
BGΔAUC(0-2h) (mg·h/dL)	Humalog LY900014	13 12	219.83 168.22	-51.61	(-95.54, -7.69)	0.0226	0.77	(0.63, 0.91)
BGΔAUC(0-5h) (mg·h/dL)	Humalog LY900014	13 12	649.06 567.79	-81.27	(-191.89, 29.35)	0.1439	0.87	(0.72, 1.06)
Adults								
BGΔAUC(0-2h) (mg·h/dL)	Humalog LY900014	14 14	145.54 112.54	-33.00	(-73.95, 7.96)	0.1108	0.77	(0.54, 1.13)
BGΔAUC(0-5h) (mg·h/dL)	Humalog LY900014	13 14	393.68 372.22	-21.46	(-127.45, 84.53)	0.6820	0.95	(0.71, 1.31)

BGΔAUC(0-Xh) = change from baseline glucose area under the concentration versus time curve from time zero to X hours postmeal. **LSM** = least-squares mean
Model: GD = Age Group + Period + Treatment + Sequence + Age Group*Treatment + Patient(Sequence) + Random Error where Patient(Sequence) is fitted as a random effect.
The CIs for the ratio were calculated using the Fieller's theorem. P-value is for the test of the mean difference

In study Part B, a total of 7 patients had a hypo/hyperglycaemic event and received intervention during the MMTT. Figure 5 presents the mean glucose excursions over time after SC bolus infusion of LY900014 and Humalog via a pump by age group. The postprandial glucose response during a 5-hour test meal period was similar between LY900014 and Humalog.

Figure 5. Study ITSA Part B: Mean glucose excursions (± SE) vs. time following a liquid mixed meal with a 0.2 U/kg SC CSII bolus dose of LY900014 or Humalog in children (upper), adolescents (middle) and adults (lower) with T1D.



2.3.4. PK/PD modelling

Introduction

The MAH has submitted several population PK (PPK) and PK/PD analysis reports in the current and prior applications:

- PPK for adults, SC injection. (Studies ITRL, ITRT, ITRR, ITRU, ITSH, ITRQ, ITRV, ITRW)
- PPK for adults, adolescents and children with T1D in study ITSA, SC injection
- PPK for adults, CSII. (Studies ITRF and ITSC)
- PPK for adults, adolescents and children with T1D in study ITSA, CSII.
- PK/PD (postprandial glucose response; liquid test meal) for adults with T1D, SC injection. (Study ITRV)
- PK/PD (postprandial glucose response; liquid test meal) for adults with T2D, SC injection. (Study ITRW)
- PK/PD (postprandial glucose response; liquid test meal) for adults, adolescents and children with T1D in study ITSA, SC injection
- PK/PD (postprandial glucose response; solid test meal) for adults with T1D, CSII (Studies ITRF and ITSC)
- PK/PD (postprandial glucose response; liquid test meal) for adults, adolescents and children with T1D in study ITSA, CSII
- In addition, PK and PK/PD simulations for SC injection for children and adolescents with T2D were conducted. No clinical studies were conducted in paediatric patients with T2D.

For the PPK models, disposition parameter estimates were fixed to the values estimated for intravenously injected LY900014 in healthy adult subjects (n=27; see PPK model for adults, SC injection). The PK/PD models utilized the Integrated Glucose-Insulin (IGI) model developed for characterizing the mechanistic feedback relationship between insulin and glucose.

Population PK modelling

Population PK: Adults, SC injection

Population Pharmacokinetic Analysis of Studies I8B-MC-ITRL, I8B-MC-ITRT, I8B-MC-ITRR, I8B-MC-ITRU, I8B-MC-ITSH, I8B-MC-ITRQ, I8B-MC-ITRV, I8B-MC-ITRW; and Exposure-Response Analysis of I8B-MC-ITRV and I8B-MC-ITRW (Approval date 15-Feb-2019)

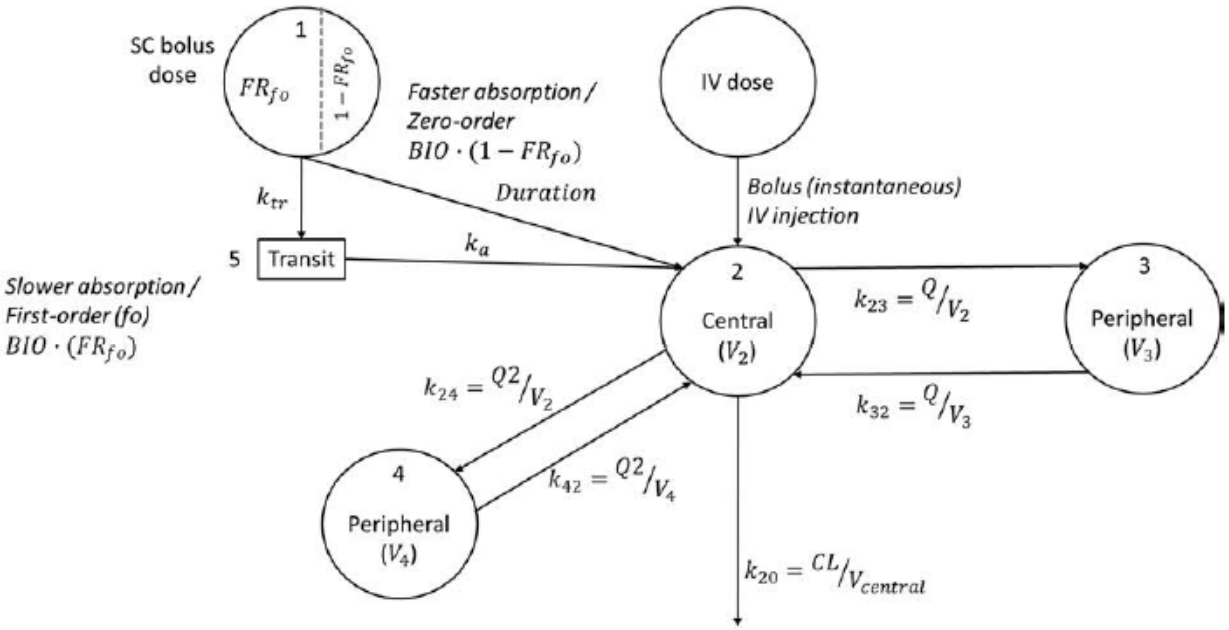
The adult population PK model for insulin lispro was developed using data from 8 clinical pharmacology studies with frequent PK sampling. A total of 18957 insulin lispro concentration-time data points from 338 subjects (149 healthy subjects, 115 T1D subjects, and 74 T2D subjects; age from 18 to 77 years and weight between 48.6 and 141.5 kg) were included in the analysis. It was assumed that once insulin lispro (the active ingredient in LY900014 and Humalog) is absorbed into the systemic circulation, the disposition parameters are the same for the two products. The model was developed in 3 steps as follows.

Model A: Disposition model for the absolute clearance and distribution parameters of insulin lispro. Data following IV injection of LY900014 in healthy subjects (n=27; study ITRT) was used. A 3-compartment disposition model provided the best description of the data. Fixed allometric exponents (0.75 for clearances;

1.0 for volumes) were used; estimated exponents were tested but they did not improve the model. Inter-individual variability (IIV) could be estimated in all of the disposition parameters with good precision (relative standard error [%RSE] ≤16.4% for all parameters). The typical CL of insulin lispro was 28.6 L/h (IIV 12.4%), the central volume (V2) was 4.73 L (IIV 6.2%), the peripheral volume 1 (V3) was 1.49 L (IIV 24.6%), and the peripheral volume 2 (V4) was 2.0 L (IIV 8.1%).

Model B: SC absorption characteristics of LY900014. The structural model for insulin lispro following IV and SC injection of LY900014 in healthy subjects and patients with T1D and T2D was developed. A combined zero-order and first-order absorption model incorporating a transit compartment best described the insulin lispro absorption following SC administration of LY900014 (Figure 6). In addition to the absorption parameters, the central volume of distribution for SC administration (V2_SC) had to be estimated to address model misspecification observed in goodness-of-fit plots. The estimated central volume was larger and more variable following SC injection than following IV injection.

Figure 6. Insulin Lispro Structural PK Model following IV and SC injection.



V_x = volume of distribution for compartment x; **CL** = clearance; **Q_x** = intercompartmental clearance for compartment x; **k_{xy}** = first-order rate constant from compartment x to y; **IV** = intravenous; **SC** = subcutaneous; **FR** = fraction; **fo** = first-order; **BIO** = bioavailability; **k_{tr}** = transit rate constant; **k_a** = first-order absorption constant.

Model C: Formulation and population effects. Once the structural and statistical model was established for IV and SC LY900014, the effects of treatment (LY900014 vs Humalog) and population differences (patients with T1D vs T2D vs healthy) were assessed on the absorption of insulin lispro and added in the structural model. A faster absorption of insulin lispro after SC administration of LY900014 compared to Humalog was observed in the clinical studies in all populations. This was best described in the model by adding treatment differences in fraction absorbed via transit compartments and first-order absorption rate constant. Population effects in the final model were included on absorption rate constant, central volume following SC administration, and bioavailability. Parameter estimates for the final population PK model are shown in Table 8. The interpretation of clinically relevant differences is summarised in Table 9.

Table 8. Insulin Lispro adult population PK model following SC administration of LY900014 and Humalog: Final model parameter estimates.

Parameter		Estimate (%RSE)		% Variability (%RSE)
Clearance (CL) (L/h)	θ_1	28.6 *fix* [a]	$\omega_{1,1}$	15.6 fix [b]
Central volume IV (V2_IV) (L)	θ_2	4.73 *fix* [a]	$\omega_{2,2}$	6.25 *fix* [a]
Central volume SC (V2_SC) (L)	θ_9	17.4 (4.7)	$\omega_{5,5}$	43.0 (5.8)
Intercompartmental clearance 1 (Q) (L/h)	θ_3	3.89 *fix* [a]	$\omega_{6,6}$	14.8 *fix* [a]
Peripheral volume 1 (V3) (L)	θ_4	1.49 *fix* [a]	$\omega_{7,7}$	24.6 *fix* [a]
Fraction absorbed via transit compartments (FR_{fo})	θ_5	0.872 fix [b]	$\omega_{9,9}$	0 *fix*
Mean transit time (MTT) (h)	θ_6	1.18 (3.4)	$\omega_{3,3}$	50 (8.3)
Duration of zero-order absorption (DUR) (h)	θ_7	0.239 (4.0)	$\omega_{4,4}$	42.2 (7.6)
Bioavailability (BIO)	θ_8	0.542 (1.7)	$\omega_{8,8}$	31.4 (11.1)
First-order absorption rate constant (K_a) (h^{-1})	θ_{10}	2.63 (14.3)	$\omega_{10,10}$	78.7 (8.2)
Intercompartmental clearance 2 (Q2) (L/h)	θ_{11}	1.73 *fix* [a]	$\omega_{11,11}$	12.5 *fix* [a]
Peripheral volume 2 (V4) (L)	θ_{12}	2.0 *fix* [a]	$\omega_{12,12}$	8.0 *fix* [a]
Differences in Humalog relative to LY900014				
Fraction absorbed via transit compartments	θ_{13}	0.14 *fix*		N/A
First-order absorption rate constant (K_a) (h^{-1})	θ_{14}	-0.597 (25.1)		N/A
Differences in patients with diabetes relative to healthy subjects				
Bioavailability for T1D	θ_{15}	-0.222 (9.8)		N/A
Bioavailability for T2D	θ_{16}	-0.0131 (224)		N/A
First-order absorption rate constant for T1D (Ka) (h^{-1})	θ_{17}	1.15 (27.5)		N/A
First-order absorption rate constant for T2D (Ka) (h^{-1})	θ_{18}	0.745 (36.9)		N/A
Central volume SC for T1D (L)	θ_{19}	0.302 (29.3)		N/A
Central volume SC for T2D (L)	θ_{20}	0.935 (15.8)		N/A
Duration of zero-order absorption T1D (h)	θ_{21}	0.296 (28.3)		N/A
Duration of zero-order absorption T2D (h)	θ_{22}	0.343 (28.3)		N/A
Proportional error (%)	$\delta_{1,1}$	34.2 (1.1)		N/A

%RSE = relative standard error of the estimate as a percentage; **N/A** = not appropriate, **IV** = intravenous administration route; **SC** = subcutaneous administration route.
a Parameter values were fixed to the estimates from the IV model for LY900014.
b Parameter values were fixed to the estimates from the IV+SC model for LY900014.

Table 9. Covariate-parameter relationships for differences between LY900014 vs Humalog and healthy subjects vs T1D vs T2D patients

PK attribute	PK parameters	Median (95%CI) Change in PK parameters*
Differences between LY900014 and Humalog		
Absorption rate	Rate of absorption via transit compartments	LY900014 absorbed 40% (30-46%) faster
	Fraction absorbed via transit compartments	100% for Humalog
		87.2% for LY900014
Differences between healthy subjects and T1D or T2D patients		
Extent of absorption	SC bioavailability relative to IV LY900014 in healthy subjects	22% (17 – 30%) lower in T1D compared to HS
		Similar for T2D and HS
Absorption rate	Rate of absorption via transit compartment compared to healthy subjects	118% (83 – 176%) faster in T1D
		74% (31 – 130%) faster in T2D
	Duration of zero-order absorption compared to healthy subjects	30% (15 – 52%) longer in T1D
		39% (26 – 73%) longer in T2D
Volume of distribution	Central volume of distribution for SC administration compared to healthy subjects	31% (12 – 57%) increase in T1D
		93% (62 – 132%) increase in T2D

* Median and 95% confidence interval based on bootstrap evaluation.

Furthermore, the effect of baseline anti-insulin lispro antibodies (ADA) on insulin lispro PK was explored using Model C. Baseline ADA were detected in 24% of subjects (1.3% of healthy subjects, 45% of T1D patients and 35% of T2D patients). A statistically significant increase of 16.5% in the insulin lispro clearance was estimated for subjects and patients with ADA detected at baseline. The ADA covariate on clearance was not added in the final PPK model, however. The grounds for this decision were that because insulins are individually dosed, the change in clearance was not expected to produce clinically meaningful difference in glycaemic control.

Population PK: Study ITSA, SC injection

Multiple Daily Injection (MDI) Pediatric/Adult Population Pharmacokinetic and Pharmacodynamic Analyses of Study I8B-MC-ITSA (Part A) (Approval Date: 21-Oct-2021)

13 children (8 to < 12 years), 14 adolescents (12 to < 18 years), and 15 adults with T1D participated in study ITSA Part A. A total of 1428 samples from 42 patients were used in the PPK model analysis.

The prior adult PPK model for SC injection was initially tested.

The PPK model for children, adolescents, and adults with T1D in Study ITSA was optimized: First, the differences between adult healthy subject's estimates and those for the patients with T1D (children, adolescents, and adults) in Study ITSA were estimated for the previously identified population covariates: SC bioavailability, zero-order duration of absorption, first-order absorption rate, and central volume of distribution. Subsequently, the difference between the first-order absorption of LY900014 and Humalog was estimated. Lastly, the allometric scaling coefficients for clearance and volume parameters were estimated. The model parameters are summarized in Table 10 and the VPCs are shown in Figure 7.

Table 10. Parameters for Insulin Lispro PK Model Following SC Administration of LY900014 and Humalog in Study ITSA and the prior Adult PK model

		Adult PK Model				Study ITSA (Part A): Children, Adolescents, and Adults with T1DM				
Parameter		Estimate (%RSE)		% Variability (%RSE)		Estimate (%RSE)		% Variability (%RSE)	Bootstrap (N=400)	
									Median	95% CI
Clearance (CL) (L/h)	θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.6 *fix*[b]	θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.6 *fix*[b]	28.6 *fix*[a]	28.6 *fix*[c]
Central volume IV (V2_IV) (L)	θ_2	4.73 *fix*[a]	$\omega_{2,2}$	6.25 *fix*[a]	θ_2	4.73 *fix*[a]	$\omega_{2,2}$	6.25 *fix*[a]	4.73 *fix*[c]	4.73 *fix*[c]
Central volume SC (V2_SC) (L)	θ_9	17.4 *fix*[c]	$\omega_{5,5}$	43.0 *fix*[c]	θ_9	17.4 *fix*[c]	$\omega_{5,5}$	43.0 *fix*[c]	17.4 *fix*[c]	17.4 *fix*[c]
Intercompartmental clearance 1 (Q) (L/h)	θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.8 *fix*[a]	θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.8 *fix*[a]	3.89 *fix*[c]	3.89 *fix*[c]
Peripheral volume 1 (V3) (L)	θ_4	1.49 *fix*[a]	$\omega_{7,7}$	24.6 *fix*[a]	θ_4	1.49 *fix*[a]	$\omega_{7,7}$	24.6 *fix*[a]	1.49 *fix*[c]	1.49 *fix*[c]
Fraction absorbed via transit compartments (FR_{S_0})	θ_5	0.872 *fix*[b]	$\omega_{9,9}$	0 *fix*	θ_5	0.872 *fix*[b]	$\omega_{9,9}$	0 *fix*	0.872 *fix*[c]	0.872 *fix*[c]
Mean transit time (MTT) (h)	θ_6	1.18 *fix*[c]	$\omega_{3,3}$	50 *fix*[c]	θ_6	1.18 *fix*[c]	$\omega_{3,3}$	50 *fix*[c]	1.18 *fix*[c]	1.18 *fix*[c]
Duration of zero-order absorption (DUR) (h)	θ_7	0.239 *fix*[c]	$\omega_{4,4}$	42.2 *fix*[c]	θ_7	0.239 *fix*[c]	$\omega_{4,4}$	42.2 *fix*[c]	0.239 *fix*[c]	0.239 *fix*[c]
Bioavailability (BIO)	θ_8	0.542 *fix*[c]	$\omega_{8,8}$	31.4 *fix*[c]	θ_8	0.542 *fix*[c]	$\omega_{8,8}$	31.4 *fix*[c]	0.542 *fix*[c]	0.542 *fix*[c]
First-order absorption rate constant (K_a) (h^{-1})	θ_{10}	2.63 *fix*[c]	$\omega_{10,10}$	78.7 *fix*[c]	θ_{10}	2.63 *fix*[c]	$\omega_{10,10}$	78.7 *fix*[c]	2.63 *fix*[c]	2.63 *fix*[c]
Intercompartmental clearance 2 (Q2) (L/h)	θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	1.73 *fix*[c]	1.73 *fix*[c]
Peripheral volume 2 (V4) (L)	θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	2.0 *fix*[c]	2.0 *fix*[c]
Differences in Humalog® relative to LY900014										
Fraction absorbed via transit compartments	θ_{13}	0.14 *fix*[b]		N/A	θ_{13}	0.14 *fix*[b]		N/A	0.14 *fix*[c]	0.14 *fix*[c]
First-order absorption rate constant (K_a) (h^{-1}) for Humalog	θ_{14}	-0.597 *fix*[c]		N/A	θ_{14}	-0.774 (7.8)		N/A	-0.772	-0.835--0.564
Differences in T1DM relative to healthy subjects										
Bioavailability for T1DM	θ_{15}	-0.222 *fix*[c]		N/A	θ_{15}	-0.39 (57)		N/A	-0.391	-0.436--0.351
First-order absorption rate constant for T1DM (K_a) (h^{-1})	θ_{17}	1.15 *fix*[c]		N/A	θ_{17}	3.58 (0.2)		N/A	3.56	1.16-4.90
Central volume SC for T1DM (L)	θ_{19}	0.302 *fix*[c]		N/A	θ_{19}	0.179 (1.6)		N/A	0.171	-0.025-0.373
Duration of zero-order absorption T1DM (h)	θ_{21}	0.296 *fix*[c]		N/A	θ_{21}	3.88 (0)		N/A	3.71	2.92-4.68
Allometric coefficient for bodyweight effect										
Clearance		0.75 *fix*[c]		N/A	θ_{23}	0.553		N/A	0.567	0.411-0.732
Central volume		1.0 *fix*[c]		N/A	θ_{24}	1.06		N/A	1.07	0.573-1.62
Proportional error (%)	$\delta_{1,1}$	34 (1.1)		N/A	$\delta_{1,1}$	35 (0)		N/A	35	31-39

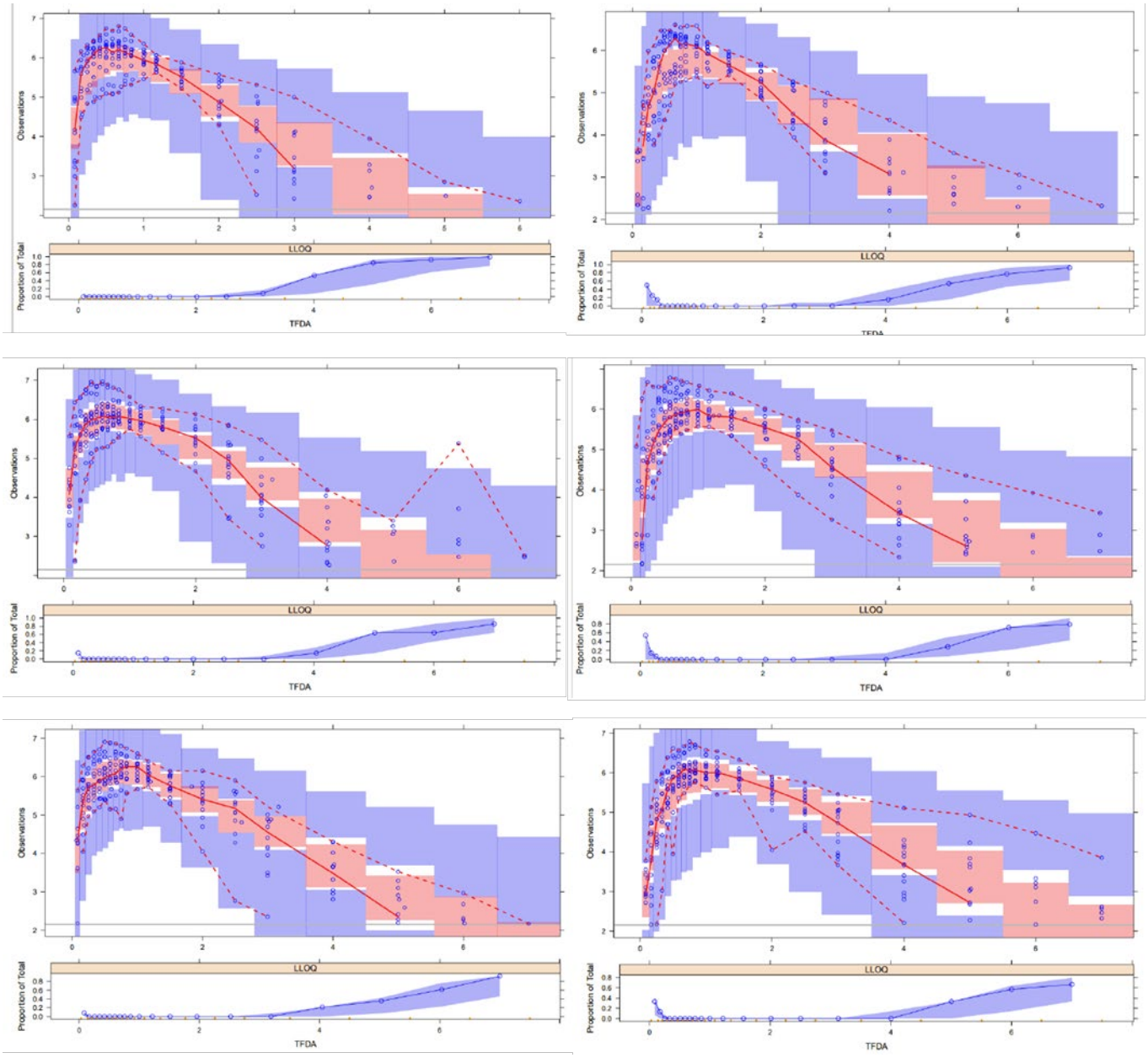
Abbreviations: CI = confidence interval; HV = healthy volunteers; IV = intravenous administration route; N =number; %RSE = relative standard error of the estimate as a percentage; PK = pharmacokinetics; N/A = not applicable; SC = subcutaneous administration route; T1DM = type 1 diabetes mellitus; T2DM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

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

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

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

Figure 7. VPCs of the model predictions of serum insulin lispro concentration following SC administration of a 0.2 U/kg dose of either LY900014 (left) or Humalog (right) in children (top), adolescent (middle), and adult (bottom) patients with T1D using the Study ITSA Part A PPK model.



Population PK model: Adults, CSII

LY900014 CSII Population Pharmacokinetic and Pharmacodynamic Report: Analyses of Studies I8B-FW-ITRF and I8B-MC-ITSC (Approval date 18-Jun-2020)

Background: Study ITRF was a single-site, 4-period, patient- and investigator-blind, randomized, replicate crossover study in adult patients with T1D to evaluate the insulin lispro PK and PD characteristics of LY900014 compared to Humalog with CSII therapy over a 3-day catheter duration via an insulin pump (Accu-Chek® Spirit; Roche). Each patient was randomized to 1 of 6 treatment sequences. Each sequence consisted of four, 3-day treatment periods comprising CSII of LY900014 or Humalog. All insulin lispro boluses were delivered with the rapid pump speed (RS) of 12 U/min as single-wave bolus given at the start of the meal. Anti-insulin lispro antibodies were detected in 19 patients at baseline.

Study ITSC was a single-site, 4-period, patient- and investigator-blind, randomized, crossover study in adult patients with T1D to evaluate the insulin lispro PK and PD characteristics of LY900014 to Humalog during CSII therapy over a 3-day catheter duration via an insulin pump (Medtronic 640G). Insulin lispro boluses were delivered as a single-wave or dual-wave bolus delivery (50% of dose as a single-wave bolus and the remaining 50% infused as a square-wave over 3 hours) with standard (1.5 U/min) bolus delivery speed (SS). Anti-insulin lispro antibodies were detected in 15 patients at baseline.

In both studies, the PK and PD samples were collected over 5 hours following an individualized solid breakfast test meal. A total of 6746 insulin lispro concentrations from 54 patients were included in the PPK analysis.

Disposition parameters of the prior structural PK model developed for SC injection therapy (see Figure 8 and Table 11) were applied to the insulin lispro CSII PPK model. The basal insulin was modelled as a zero-order infusion with fixed disposition parameter estimates, except for the central volume of distribution that was estimated together with the prandial insulin data. For prandial insulin, all absorption parameters and central volume of distribution were estimated. To account for the observed differences in the rate of absorption of LY900014 vs. Humalog, pump delivery speed (rapid speed (RS) vs. standard speed (SS)), and catheter dwell time (Day 1 vs. Day 3), separate ka with interindividual variability was estimated with the following discrete categories:

- LY900014 on Day 1 for Study ITSC (SS)
- Humalog on Day 1 for Study ITSC (SS)
- LY900014 on Day 3 for Study ITSC (SS)
- Humalog on Day 3 for Study ITSC (SS)
- LY900014 on Day 1 for Study ITRF (RS)
- Humalog on Day 1 for Study ITRF (RS)
- LY900014 on Day 3 for Study ITRF (RS)
- Humalog on Day 3 for Study ITRF (RS)

Graphical analyses of the individual parameter estimates and random effects did not identify any additional covariate relationships to evaluate in the PK model. The final model parameter estimates are summarized in Table 12. Prediction- and variability-corrected VPCs (500 simulated datasets) indicated adequate model fit to the observed data (Figure 9).

Table 11. Insulin Lispro PK Model for adult patients with T1D on CSII Therapy

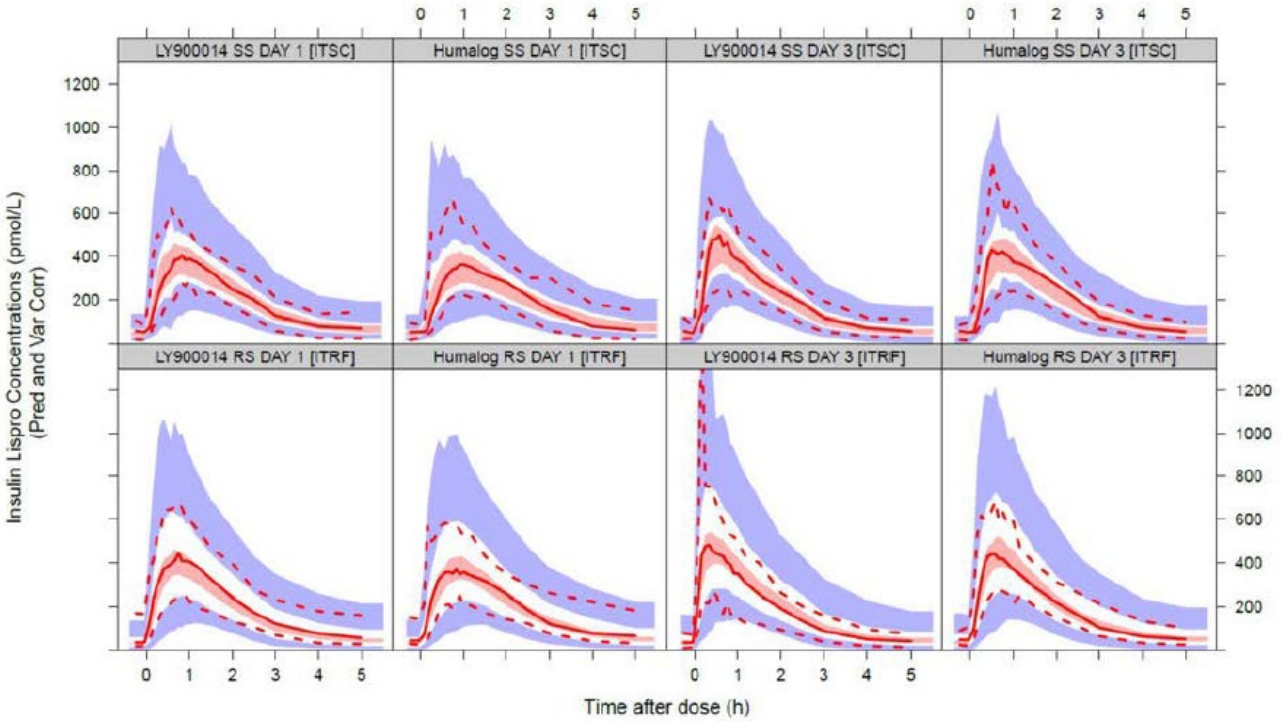
Parameter		Estimate (%RSE)		% Variability (%RSE)[b]		Bootstrap median	Bootstrap 95% CI		Bootstrap median	Bootstrap 95%CI
Clearance (CL) (L/h)	θ_1	28.6 *fix*[a]	$\omega_{1,1}$	15.7 *fix*[a]	θ_1	N/A	N/A	$\omega_{1,1}$	N/A	N/A
Central volume SC (V2) (L)	θ_9	3.27 (15.4)	$\omega_{5,5}$	146.9 (10.0)	θ_9	3.3	2.64, 4.1	$\omega_{5,5}$	119	91.1, 163
Intercompartmental clearance 1 (Q) (L/h)	θ_3	3.89 *fix*[a]	$\omega_{6,6}$	14.9 *fix*[a]	θ_3	N/A	N/A	$\omega_{6,6}$	N/A	N/A
Peripheral volume 1 (V3) (L)	θ_4	1.49 *fix*[a]	$\omega_{7,7}$	25.0 *fix*[a]	θ_4	N/A	N/A	$\omega_{7,7}$	N/A	N/A
Intercompartmental clearance 2 (Q2) (L/h)	θ_{11}	1.73 *fix*[a]	$\omega_{11,11}$	12.5 *fix*[a]	θ_{11}	N/A	N/A	$\omega_{11,11}$	N/A	N/A
Peripheral volume 2 (V4) (L)	θ_{12}	2.0 *fix*[a]	$\omega_{12,12}$	8.0 *fix*[a]	θ_{12}	N/A	N/A	$\omega_{12,12}$	N/A	N/A
Fraction absorbed via transit compartments (FR_{fb})	θ_5	0.859 (1.2)	$\omega_{9,9}$	7.1 (15.6)	θ_5	0.856	0.826, 0.891	$\omega_{9,9}$	5.85	3.12, 8.5
Mean transit time (MTT) (h)	θ_6	2.07 (4.5)	$\omega_{3,3}$	31.6 (21.8)	θ_6	2.07	1.9, 2.26	$\omega_{3,3}$	31.5	20.8, 39.5
Duration of zero-order absorption (h)										
Prandial insulin	θ_7	2.49 (1.3)	$\omega_{4,4}$	7.1 *fix*[a]	θ_7	2.5	2.39, 2.63	$\omega_{4,4}$	N/A	N/A
Basal insulin ITSC	θ_{16}	84 (5)	$\omega_{13,13}$	33.9 (15.5)	θ_{16}	83.4	73.1, 98.3	$\omega_{13,13}$	33.3	19.5, 44.9
Basal insulin ITRF Day 1	θ_{17}	57.6 (5.9)	$\omega_{14,14}$	36.5 (35.1)	θ_{17}	57.9	49.6, 64.7	$\omega_{14,14}$	35.7	23.7, 45.2
Basal insulin ITRF Day 3	θ_{18}	87.7 (8.5)	$\omega_{15,15}$	53.7 (13.1)	θ_{18}	93.9	78.3, 112	$\omega_{15,15}$	56.4	23.9, 78.4
Bioavailability prandial insulin (BIO)	θ_8	0.423 (1.8)	$\omega_{8,8}$	16.6 (25.7)	θ_8	0.424	0.402, 0.443	$\omega_{8,8}$	14.4	5.34, 26.5
First-order absorption rate constant (k_a) (h^{-1})										
LY900014 ITSC on Day 1 (SS)	θ_{10}	3.04 (11.1)	$\omega_{10,10}$	75.9 (11.6)	θ_{10}	2.91	2.05, 4.08	$\omega_{10,10}$	71.1	43.2, 108
Humalog ITSC on Day 1 (SS)	θ_{13}	1.79 (9.8)	$\omega_{16,16}$	68.3 (14.8)	θ_{13}	1.76	1.3, 2.38	$\omega_{16,16}$	64.8	38.7, 108
LY900014 ITSC on Day 3 (SS)	θ_{14}	6.57 (0.8)	$\omega_{17,17}$	4 (13.2)	θ_{14}	6.1	5.19, 7.35	$\omega_{17,17}$	7.52	1.83, 31.3
Humalog ITSC on Day 3 (SS)	θ_{15}	3.09 (6.2)	$\omega_{18,18}$	39.8 (31.6)	θ_{15}	3.02	2.46, 3.8	$\omega_{18,18}$	38	19.1, 55.6
LY900014 ITRF on Day 1 (RS)	θ_{19}	3.91 (7.9)	$\omega_{19,19}$	47.1 (22.5)	θ_{19}	3.88	3.15, 5.21	$\omega_{19,19}$	46	26.3, 67.5
Humalog ITRF on Day 1 (RS)	θ_{20}	2.29 (6.1)	$\omega_{20,20}$	37.4 (22.2)	θ_{20}	2.29	1.94, 2.71	$\omega_{20,20}$	36.2	21, 50.1
LY900014 ITRF on Day 3 (RS)	θ_{21}	19.1 (14.4)	$\omega_{21,21}$	110.3 (7.8)	θ_{21}	19.7	12.3, 55.6	$\omega_{21,21}$	118	40.9, 270
Humalog ITRF on Day 3 (RS)	θ_{22}	4.07 (6.9)	$\omega_{22,22}$	38.0 (22.3)	θ_{22}	4.08	3.31, 5.05	$\omega_{22,22}$	36.7	21.9, 50.5
Proportional error (%)	$\delta_{1,1}$	24.9 (2.2)[c]		N/A	$\delta_{1,1}$	25.4	23.4, 27.6		N/A	N/A

CI = confidence interval; **CSII** = continuous subcutaneous insulin infusion; **CV** = coefficient of variation; **IV** = intravenous; **N/A** = not appropriate; **%RSE** = relative standard error of the estimate as a percentage; **RS** = rapid single-wave; **SC** = subcutaneous; **SS** = standard single-wave.
a Parameter values were fixed to the estimates from the IV model for LY900014.
b Reported as %CV, calculated by equation:

$$100 \cdot \sqrt{e^{\omega^2} - 1},$$

where ω^2 is the NONMEM output for the inter-subject variability of the parameter.
c Standard error for the raw $\delta_{1,1}$ value.

Figure 8. Visual predictive check of the model predictions of serum insulin lispro concentration following administration of a standard single-wave bolus (top row) or a rapid single-wave bolus (bottom row) of LY900014 or Humalog.



RS = rapid single-wave; **SS** = standard single-wave; **TFDA** = time from dose administration.
The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed lines represent the observed 2.5 and 97.5 percentiles, while blue shaded areas represent simulated 95% confidence interval of the same.

Population PK model: Study ITSA, CSII

Continuous Subcutaneous Insulin Infusion (CSII) Pediatric/Adult Population Pharmacokinetic and Pharmacodynamic Analyses of Study: I8B-MC-ITSA Part B (Approval date 09-Nov-2021)

LY900014 and Humalog were administered via a single wave bolus with a standard delivery speed (1.5 U/minute) in study ITSA Part B. PK data were available from 12 children (8 to < 12 years), 13 adolescents (12 to < 18 years), and 12 adults with T1D in study ITSA Part B. A total of 1296 samples from 37 patients were used in the PPK model analysis.

Based on the PPK model optimization for Study ITSA Part A (see above), PK parameters for SC bioavailability, zero-order duration of absorption, first-order absorption rate, fraction absorbed via transit compartments, mean transit time, and central volume of distribution were estimated for children, adolescents, and adults with T1D in Study ITSA Part B. Lastly, the allometric scaling coefficients for clearance and volume parameters were estimated. The model parameters are summarized in Table 12 and the VPCs are shown in Figure 10.

Table 12. PK Parameters for insulin lispro model following subcutaneous infusion of LY900014 and Humalog via CSII in children, adolescents, and adults with T1D in Study ITSA Part B

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

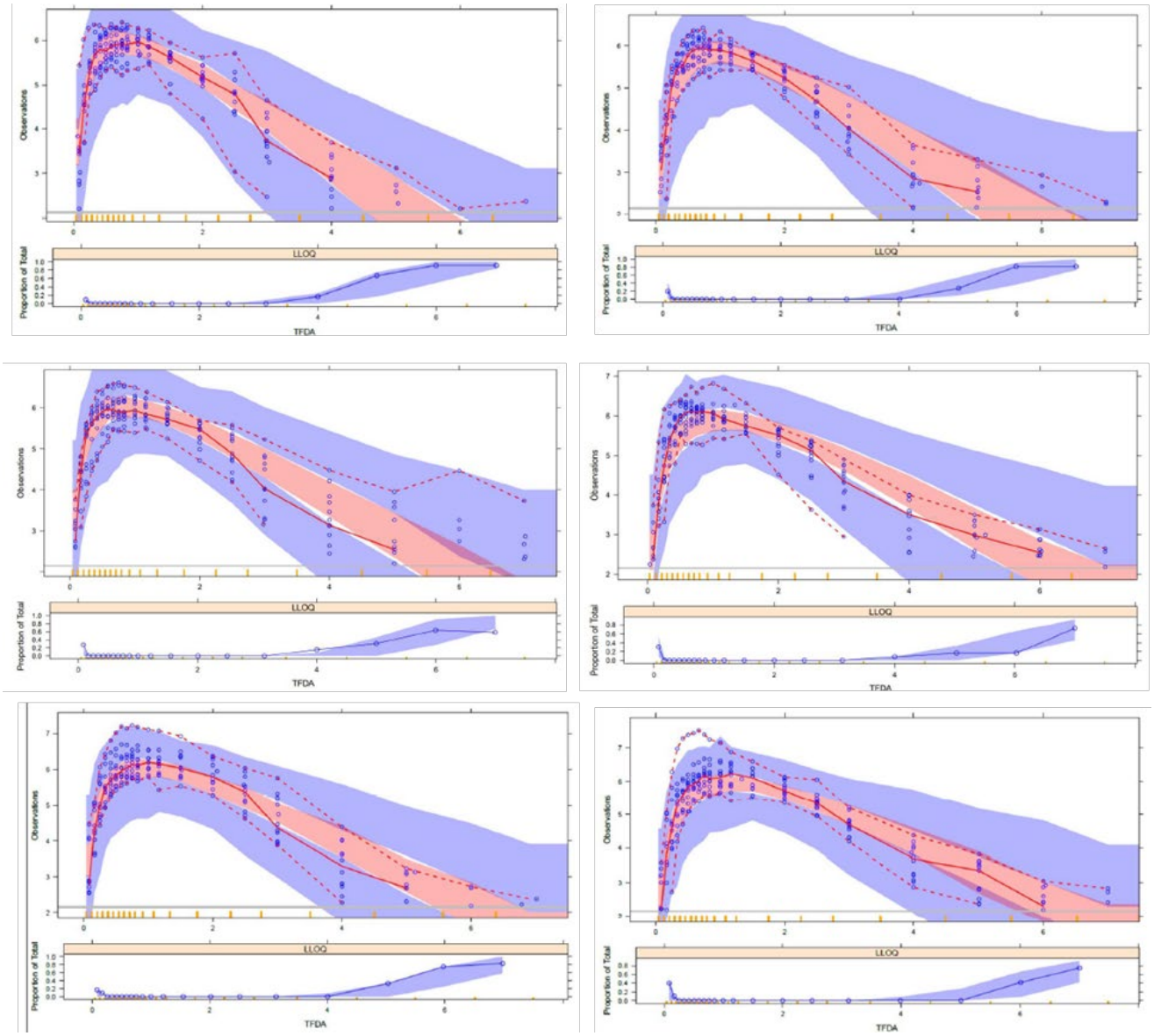
Abbreviations: CSII = continuous subcutaneous insulin infusion; IV = intravenous; N/A = not applicable; PK = pharmacokinetics; %RSE = relative standard error of the estimate as a percentage; RS = rapid speed; SC = subcutaneous; SS = standard speed; T1DM = type 1 diabetes mellitus.

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

[b] Parameter values were fixed to the adult pump PK model.

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

Figure 9. VPCs of the model predictions of serum insulin lispro concentration following SC infusion of a 0.2 U/kg dose of either LY900014 (left) or Humalog (right) in children (top), adolescent (middle), and adult (bottom) patients with T1D using the Study ITSA Part B PPK model.



PK/PD model: PPG after liquid test meal, adults with T1D or T2D, SC injection

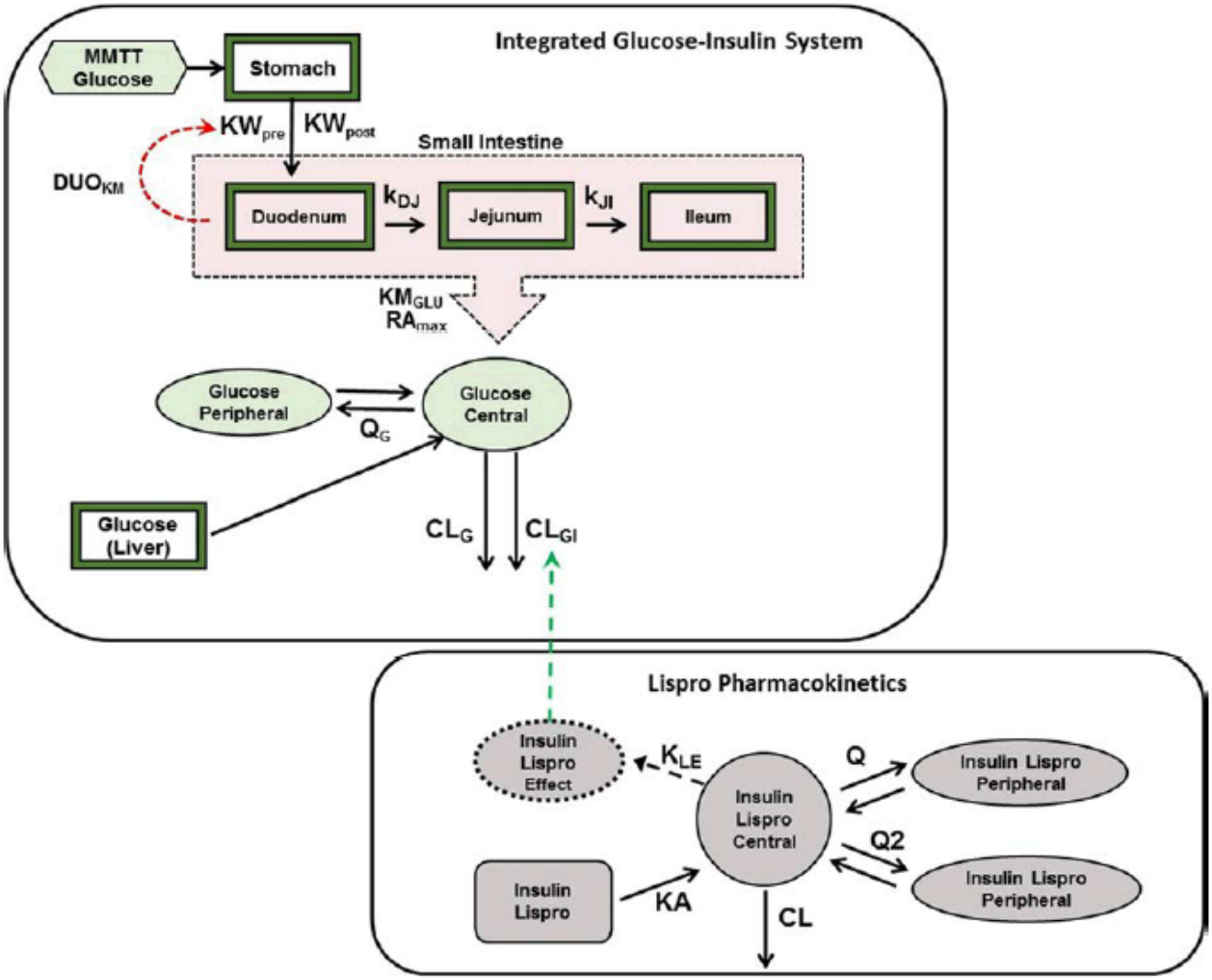
Population Pharmacokinetic Analysis of Studies I8B-MC-ITRL, I8B-MC-ITRT, I8B-MC-ITRR, I8B-MC-ITRU, I8B-MC-ITSH, I8B-MC-ITRQ, I8B-MC-ITRV, I8B-MC-ITRW; and Exposure-Response Analysis of I8B-MC-ITRV and I8B-MC-ITRW (Approval date 15-Feb-2019)

A sequential PK/PD modelling approach was used to analyze the postprandial glucose response after a liquid test meal in adult patients with T1D (Study ITRV) and T2D (Study ITRW). See above for description of the population PK model utilized in these analyses. The individual PK parameters from the final insulin lispro PK model were merged with the PD dataset to predict the time course of insulin concentrations for the exposure-response modelling.

The relationship between LY900014 and Humalog administration, insulin concentrations in serum, and the corresponding effect on glucose concentrations was evaluated using an exposure-response model that

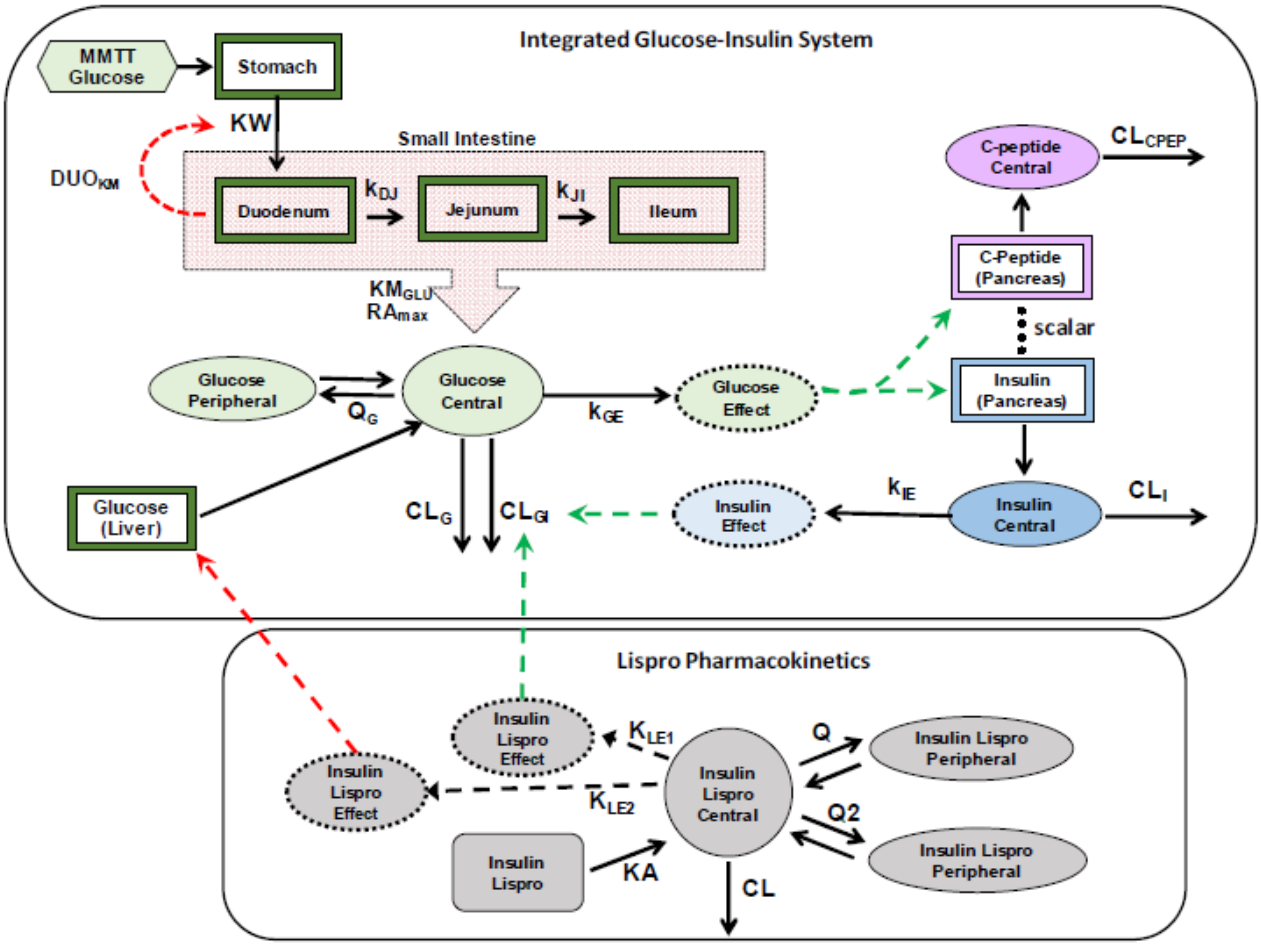
utilizes the Integrated Glucose-Insulin (IGI) model. The IGI model is a (semi)mechanistic PK/PD model initially developed using data from T2D patients and healthy subjects undergoing intravenous and oral glucose tolerance tests. Subsequently, gastric emptying and intestinal transit times have been incorporated in the model. In brief, the model incorporates the effects of endogenous glucose and insulin (the stimulatory effect of glucose on insulin production; the stimulatory effect of insulin on glucose elimination; the inhibitory effect of glucose and insulin on hepatic glucose production; the glucose absorbed into the body was calculated from carbohydrate contents in the meals). The IGI model was linked to a model for small intestinal transit through the stomach, duodenum and ileum that incorporated inhibition of gastric emptying by glucose, and saturable absorption of glucose through the epithelium to account for gastric emptying and glucose absorption. Additionally, the exogenous insulin effect on glucose clearance was described using a nonlinear (sigmoidal Emax model) relationship between insulin and insulin-dependent glucose clearance. The base structure of the IGI model for T1D and T2D are shown in Figures 5.3.4.6 and 5.3.4.7, respectively. Parameter estimates of the final optimized IGI model for T1D and T2D are summarized in Tables 5.3.4.6 and 5.3.4.7, respectively.

Figure 10. Base Structure of the IGI model for T1D patients



CL = insulin lispro clearance; **CL_G** = insulin independent glucose clearance; **CL_{GI}** = endogenous insulin dependent glucose clearance; **DUO_{KM}** = amount of glucose in duodenum giving 50% of maximum inhibition of gastric emptying; **KA** = insulin lispro first-order absorption rate constant; **k_{DJ}** = rate constant for glucose movement from duodenum to jejunum; **k_{JI}** = rate constant for glucose movement from jejunum to ileum; **k_{LE}** = rate constant for insulin lispro effect compartment related to CL_{GI}; **KM_{GLU}** = amount of glucose giving 50% of maximum absorption; **KW_{pre}** = gastric emptying rate for premeal dosing; **KW_{post}** = gastric emptying rate for meal for post meal dosing; **MMTT** = mixed meal tolerance test; **Q** = intercompartmental clearance between insulin lispro central compartment and peripheral compartment 1; **Q2** = intercompartmental clearance between insulin lispro central compartment and peripheral compartment 2; **RA_{max}** = maximum rate of absorption from small intestine.

Figure 11. Base Structure of the IGI model for T2D



MMTT=mixed meal tolerance test; **KM_{GLU}** = amount of glucose giving 50% of maximum absorption; **RA_{max}** = maximum rate of absorption from small intestine; **KW** = gastric emptying rate; **DUO_{KM}**= amount of glucose in duodenum giving 50% of maximum inhibition of gastric emptying; **k_{DJ}** = rate constant for glucose movement from duodenum to jejunum; **k_{JI}** = rate constant for glucose movement from jejunum to ileum; **Q_G** = intercompartmental clearance between glucose central and glucose peripheral compartments; **k_{GE}** = rate constant for glucose effect compartment; **CL_G** = insulin-independent glucose clearance; **CL_{GI}** = insulin dependent glucose clearance; **CL_{CPEP}** = C-peptide clearance; **k_{IE}** = rate constant for endogenous insulin effect compartment; **CL_I** = endogenous insulin clearance; **KA** = insulin lispro absorption rate; **K_{LE1}** = rate constant for insulin lispro effect compartment related to CLGI; **K_{LE2}** = rate constant for insulin lispro effect compartment related to hepatic glucose production; **Q** = clearance between insulin lispro central compartment and peripheral compartment 1; **Q2** = clearance between insulin lispro central compartment and peripheral compartment 2;
CL = insulin lispro clearance.

Table 13. Parameter Estimates of the Final Optimized IGI Model for adult T1D patients (Study ITRV)

Model		Optimized			
Parameter		**Estimate (%RSE)**	**IIV (%CV)**	**Bootstrap Median (95%CI)**	**Bootstrap IIV (%CV)**
Gastric emptying					
Emptying rate pre-dose (/min) (KW_{pre})	θ_{19}	0.0458 *fix* [g]	135 *fix* [g]	0.0458 *fix* [g]	135 *fix* [g]
Emptying rate post-dose (/min) (KW_{post})	θ_{20}	0.167 *fix* [g]	135 *fix* [g]	0.167 *fix* [g]	135 *fix* [g]
Amount of glucose giving 50% of inhibition (cg) (DUO_{KM})	θ_2	474 (13.3)	73.3 (10.2)	492 (326, 674)	66.4 (19.9, 134)
Shape parameter for glucose inhibition (GAMMA)	θ_3	14 *fix* [a]	7.1 *fix* [f]	14 *fix* [a]	7.1 *fix* [f]
Delay in emptying for the meal (min)	θ_8	0.0368 *fix* [e]	7.1 *fix* [f]	0.0368 *fix* [e]	7.1 *fix* [f]
Glucose absorption					
Maximum rate of absorption from duodenum (cg/h)	θ_{13}	3480 *fix* [a]	7.1 *fix* [f]	3480 *fix* [a]	7.1 *fix* [f]
Maximum rate of absorption from jejunum (cg/h)	θ_{14}	12400 *fix* [a]	7.1 *fix* [f]	12400 *fix* [a]	7.1 *fix* [f]
Maximum rate of absorption from ileum (cg/h)	θ_{15}	7980 *fix* [a]	7.1 *fix* [f]	7980 *fix* [a]	7.1 *fix* [f]
Amount of glucose giving 50% of maximum absorption (cg) (KM_{GLU})	θ_{12}	2290 (8.7)	7.1 *fix* [f]	2320 (1490,4130)	7.1 *fix* [f]
First pass effect on glucose	θ_1	0.80 *fix* [b]	7.1 *fix* [f]	0.80 *fix* [b]	7.1 *fix* [f]
Glucose disposition					
Insulin-independent glucose clearance (L/h)	θ_4	1.89 *fix* [e]	59.3 *fix* [d]	1.89 *fix* [e]	59.3 *fix* [d]
Maximum insulin-dependent glucose clearance (L/h)	θ_5	21.8 *fix* [e]	54.0 *fix* [e]	21.8 *fix* [e]	54.0 *fix* [e]
Central volume of distribution (L)	θ_6	9.33 *fix* [c]	7.1 *fix* [f]	9.33 *fix* [c]	7.1 *fix* [f]
Peripheral volume of distribution (L)	θ_7	8.56 *fix* [c]	7.1 *fix* [f]	8.56 *fix* [c]	7.1 *fix* [f]
Intercompartmental clearance (L/h)	θ_9	26.5 *fix* [c]	7.1 *fix* [f]	26.5 *fix* [c]	7.1 *fix* [f]
Rate constant for glucose effect compartment (/h) (K_{LE})	θ_{10}	2.1 *fix* [e]	7.1 *fix* [f]	2.1 *fix* [e]	7.1 *fix* [f]
Formation of endogenous glucose during the meal period (mg)	θ_{16}	4.79 (14)	7.1 *fix* [f]	5.54 (4.33, 7.51)	7.1 *fix* [f]
Concentration of insulin lispro giving 50% of maximum insulin-dependent glucose clearance (pmol/mL)	θ_{17}	338 (9.4)	7.1 *fix* [f]	329 (253, 497)	7.1 *fix* [f]
Shape parameter for insulin lispro	θ_{18}	1.86 (10.4)	7.1 *fix* [f]	1.9 (1.37, 2.36)	7.1 *fix* [f]
Residual variability (%)	θ_{11}	22.2 (1.4)		21.9 (18.3, 25.0)	

Abbreviations: %RSE = relative standard error of the estimate as a percentage; CI = confidence interval; T1DM = type 1 diabetes mellitus.

a Fixed to value from Alskär et al. 2016.

b Fixed to value from Hovorka et al. 2004.

c Fixed to value from Silber et al. 2010.

d Fixed to value from Schneck et al. 2013.

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

f Fixed to facilitate efficient operation of the SAEM algorithm.

g Fixed to value from sensitivity analysis.

Table 14. Parameter Estimates of the Optimized IGI Model for T2D (Study ITRW)

Parameter		Estimate (%RSE)	IIV %CV	Bootstrap Median (95%CI)	Bootstrap IIV %CV (95% CI)
Gastric emptying					
Emptying rate (1/min) (KW)	θ_{28}	0.00886 (19)	50.0 fix [a]	0.00545 (0.00173 – 0.0132)	50.0 fix [a]
Amount of glucose in duodenum giving 50% of inhibition (cg) (DUO_{KM})	θ_{22}	557 (9.4)	32.9 fix [f]	581 (447 – 1130)	32.9 fix [f]
Shape parameter for intestinal glucose inhibition of gastric emptying	θ_{23}	14 fix [a]	5.0 fix [f]	14 fix [a]	5.0 fix [f]
Delay in emptying for the meal (min)	θ_{7}	0 fix [b]	0 fix [b]	0 fix [b]	0 fix [b]
Glucose absorption					
Maximum rate of absorption from duodenum (cg/h)	θ_{19}	3480 fix [a]	21.0 fix [f]	3480 fix [a]	21.0 fix [f]
Maximum rate of absorption from jejunum (cg/h)	θ_{20}	12400 fix [a]	24.0 fix [f]	12400 fix [a]	24.0 fix [f]
Maximum rate of absorption from ileum (cg/h)	θ_{21}	7980 fix [a]	52.0 fix [f]	7980 fix [a]	52.0 fix [f]
Amount of glucose giving 50% of maximum absorption (cg) (KM_{GLU})	θ_{4}	1760 (6.1)	32.4 fix [f]	2150 (1100 – 9660)	32.4 fix [f]
First pass effect on glucose	–	1 fix [a,b]	0 fix [b]	1 fix [a,b]	0 fix [b]
Glucose disposition					
Mean glucose concentration at meal start (mg/dL)	–	136 [c]	5.3 [c]	--	--
Insulin-independent glucose clearance (L/h) (CL_G)	θ_{3}	1.72 fix [d]	59.1 fix [d]	1.72 fix [d]	59.1 fix [d]
Endogeneous insulin-dependent glucose clearance (L/h)/(pmol/L) (CL_{GI})	θ_{16}	0.0743 fix [d]	48.3 fix [d]	0.0743 fix [d]	48.3 fix [d]
Central volume of distribution (L) (V_G)	θ_{1}	9.33 fix [d,e]	30.1 fix [d]	9.33 fix [d,e]	30.1 fix [d]
Peripheral volume of distribution (L) (V_P)	θ_{6}	8.56 fix [d]	30.1 fix [d]	8.56 fix [d]	30.1 fix [d]
Intercompartmental clearance (L/h) (Q_G)	θ_{2}	26.5 fix [d]	85.1 fix [d]	26.5 fix [d]	85.1 fix [d]
Rate constant for glucose effect compartment (1/h) (k_{GE})	θ_{18}	0.738 fix [d]	53.1 fix [d]	0.738 fix [d]	53.1 fix [d]
Steady-state glucose concentration (mg/dL) (GSS)	θ_{8}	156 (8.4)	32.1	153 (132 – 178)	32.1 (17.7 – 42.5)
Maximum glucose clearance dependent on insulin lispro (L/h)	θ_{12}	0.0629 (9.5)	32.4 fix [f]	0.0332 (0.00943 – 0.161)	32.4 fix [f]

Parameter		Estimate (%RSE)	IIV %CV	Bootstrap Median (95%CI)	Bootstrap IIV %CV (95% CI)
Glucose disposition (continued)					
Concentration of insulin lispro giving 50% of maximum glucose clearance dependent on insulin lispro (pmol/L)	Θ_{11}	64.1 (3.2)	15.1 fix [f]	50.0 (19.5 – 94.4)	15.1 fix [f]
Shape parameter for insulin lispro relationship with glucose clearance	Θ_{10}	1.25 (1.4)	5.0 fix [f]	1.41 (1.05 – 1.73)	5.0 fix [f]
Rate constant for insulin lispro effect compartment on glucose clearance (1/h) (K_{LE1})	Θ_{9}	0.815 (1.9)	5.0 fix [f]	0.566 (0.392 – 0.832)	5.0 fix [f]
Concentration of insulin lispro giving 50% of maximum inhibition of EGP (pmol/L)	Θ_{31}	51.9 (2.1)	15.1 fix [f]	46.2 (27.9 – 77.9)	15.1 fix [f]
Shape parameter for insulin lispro inhibition of EGP	Θ_{30}	2.20 (0.6)	5.0 fix [f]	2.78 (2.05 – 3.87)	5.0 fix [f]
Rate constant for insulin lispro effect compartment on EGP (1/h) (K_{LE2})	Θ_{29}	0.507 (1.4)	5.0 fix [f]	0.464 (0.330 – 0.834)	5.0 fix [f]
Glucose residual variability (%)	Θ_{32}	13.7 (1.0)	--	13.4 (12.1 – 14.8)	--
C-peptide disposition					
Mean c-peptide concentration at meal start (pmol/L)	–	508 [c]	41.8 [c]	--	--
Volume of distribution (mL) (V_{CP})	Θ_{25}	69.3[e] (7.5)	32.4 fix [f]	48.2 (13.5 – 234)	32.4 fix [f]
Clearance (L/h) (CL_{CP})	Θ_{26}	102 (4.3)	32.4 fix [f]	63.0 (8.65 – 200)	32.4 fix [f]
Steady-state c-peptide concentration (pmol/L)	Θ_{27}	898 (12.9)	121.6	870 (598 – 1200)	116 (66.0 – 215)
Fractional scalar of baseline c-peptide relative to baseline insulin	Θ_{24}	0.373 (5.3)	15.9 fix [f]	0.247 (0.0419 – 0.439)	15.9 fix [f]
C-peptide residual variability (%)	Θ_{33}	22.8 (1.7)	--	22.5 (19.0 – 26.0)	--
Endogenous insulin disposition					
Steady-state insulin concentration (pmol/L) (ISS)	Θ_{13}	113 (10.6)	49.1 fix [d]	102 (75.4 – 135)	49.1 fix [d]
Volume of distribution (L) (V_I)	Θ_{3}	6.09 fix [d,e]	41.1 fix [d]	6.09 fix [d,e]	41.1 fix [d]
Clearance (L/h) (CL_I)	Θ_{14}	73.2 fix [d]	29.0 fix [d]	73.2 fix [d]	29.0 fix [d]
Rate constant for endogenous insulin effect compartment on CL_{GI} (1/h) (k_{IE})	Θ_{17}	0.464 fix [d]	44.9 fix [d]	0.464 fix [d]	44.9 fix [d]
Control parameter for the glucose effect on endogenous insulin secretion (IPRG)	Θ_{15}	1.91 (5.7)	35.1 fix [d]	1.96 (1.62 – 2.36)	35.1 fix [d]
Parameter Correlation					
Corr V_G-Q_G	–	– 0.75 fix [d]	--	--	--
Corr V_G-V_I	–	0.71 fix [d]	--	--	--
Corr Q_G-V_I	–	– 0.35 fix [d]	--	--	--

Abbreviations: %RSE = relative standard error of the estimate as a percentage; IIV = inter-individual variability; %CV = coefficient of variation as a percentage; cg = centigram (cg/L = mg/dL); CI = confidence interval; EGP = endogenous glucose production; Corr = correlation; T2DM = type 2 diabetes mellitus.

a Fixed to value from Alskär et al. 2016.

b Fixed to value after estimation caused model performance issues (eg. model instability, unreliable parameter estimate, parameter estimate deemed to have minimal impact on model fit).

c Reported as mean and %CV of observations.

d Fixed to value from Jauslin et al. 2011.

e Reported for 70 kg individual. Model incorporated allometric scaling: Vd = Θ x WT/70, where Vd is the volume of distribution of an individual, Θ is the population parameter estimate, and WT is the body weight (kg) of an individual. Study ITRW median baseline body weight = 96.9 kg.

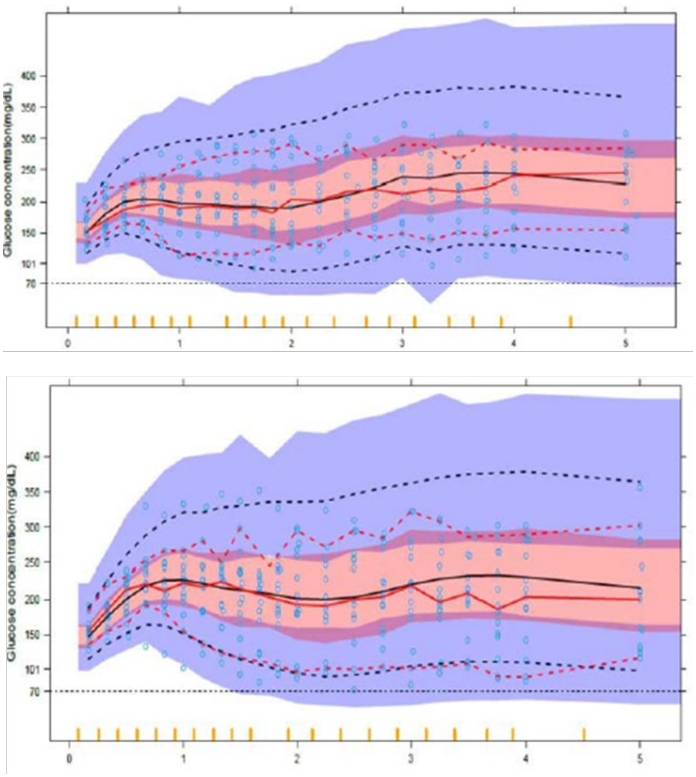
f Fixed to value deemed reasonable to facilitate efficient operation of the SAEM algorithm and based on information reported in Jauslin et al 2011.

PK/PD model: PPG after liquid test meal, Study ITSA, SC injection

The final optimized PK/PD model for adults with T1D (Study ITRV) was tested first. The model was then optimized using the glucose data only from the adults in Study ITSA Part A (n = 14) to address any study differences between Studies ITRV and ITSA.

In the optimized adult model for study ITSA Part A, the KW_{pre}, DUO_{KM}, KM_{GLU}, EC50, HILL, and CL_{GI} parameter values were estimated simultaneously, as well as the IIV for DUO_{KM}, CL_{GI}, and the residual variability. The VPCs for LY900014 and Humalog in adults showed good agreement between the median of the observed and median of the simulated glucose concentrations (Figure 12). However, even the optimized adult ITSA Part A model underpredicted the glucose concentrations observed in Study ITSA Part A for the children and adolescents (Figures 5.3.4.10 and 5.3.4.11, respectively). The model was considered to describe the data well and no further model development conducted. The final model parameters are summarized in Table 15.

Figure 12. VPC of the model predictions of glucose concentration during the liquid MMTT following administration of LY900014 (top) and Humalog (bottom) immediately prior to the start of the meal in adults with T1D for the optimized adult model (Study ITSA Part A).

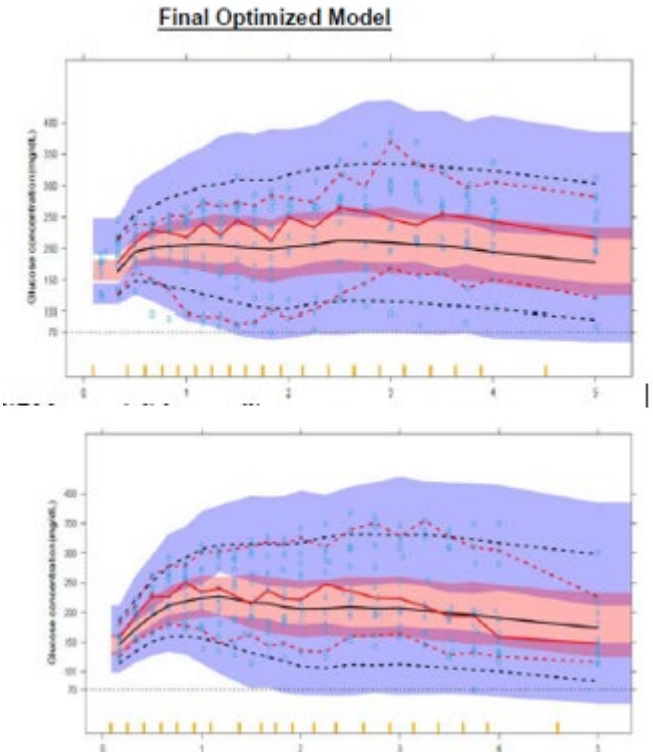


The blue circles represent observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed red lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same. The solid black line represents the median of the prediction interval, and the black dashed lines represent the lower and upper bounds of the 90% prediction interval.

Figure 13. VPC of the model predictions of glucose concentration during the liquid MMTT following administration of LY900014 (top) and Humalog (bottom) immediately prior to the start of the meal in children with T1D for the final optimized model (Study ITSA Part A).

Optimized Adult Model

Final Optimized Model

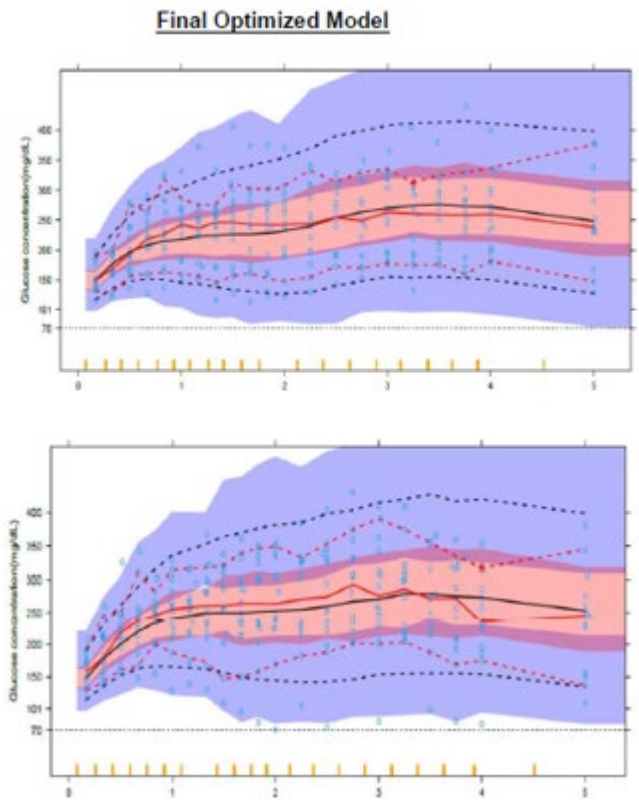


The blue circles represent observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed red lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same. The solid black line represents the median of the prediction interval, and the black dashed lines represent the lower and upper bounds of the 90% prediction interval.

Figure 14. VPC of the model predictions of glucose concentration during the liquid MMTT following administration of LY900014 (top) and Humalog (bottom) immediately prior to the start of the meal in adolescents with T1D for the final optimized model (Study ITSA Part A).

Optimized Adult Model

Final Optimized Model



The blue circles represent observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The dashed red lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same. The solid black line represents the median of the prediction interval, and the black dashed lines represent the lower and upper bounds of the 90% prediction interval.

Table 15. Parameter Estimates of the Optimized IGI Model for T1D (Study ITSA Part A)

Model		**Prior Adult T1DM IGI Model**		**Study ITSA (Part A): Children, Adolescents, and Adults with T1DM**			
Parameter		**Estimate (%RSE)**	**IIV (%CV)**	**Estimate (%RSE)**	**IIV (%CV)**	**Bootstrap Median (95% CI)**	**Bootstrap IIV (%CV)**
Gastric emptying							
Emptying rate predose (/min) (KW_{pre})	θ19	0.0458 *fix*[g]	135 *fix*[g]	0.0207 (7.6)	135 *fix*[g]	0.0200 (0.0086, 0.0306)	135 *fix*[g]
Emptying rate postdose (/min) (KW_{post})	θ20	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]
Amount of glucose in the duodenum giving 50% of maximum inhibition of gastric emptying (cg) (DUOKM)	θ2	474 (13.3)	73.3 (10.2)	188 (8.3)	42	173 (147, 221)	47 (22, 66)
Shape parameter for glucose inhibition (GAMMA)	θ3	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]
Delay in emptying for the meal (min)	θ8	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]
Glucose absorption							
Maximum rate of absorption from the duodenum (cg/h)	θ13	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]
Maximum rate of absorption from the jejunum (cg/h)	θ14	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]
Maximum rate of absorption from the ileum (cg/h)	θ15	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]
Amount of glucose giving 50% of maximum absorption (cg) (KM_{GLU})	θ12	2290 (8.7)	7.1 *fix*[f]	127 (6.2)	7.1 *fix*[f]	112 (89.1, 154)	7.1 *fix*[f]
First-pass effect on glucose	θ1	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]
Glucose disposition							
Insulin-independent glucose clearance (L/h)	θ4	1.89 *fix*[e]	59.3 *fix*[d]	1.89 *fix*[e]	59.3 *fix*[d]	1.89 *fix*[e]	59.3 *fix*[d]
Maximum insulin-dependent glucose clearance (L/h) Adult		21.8 *fix*[e]	54.0 *fix*[e]	11.4 (20)	75	11.7 (7.53, 15.0)	65 (25-104)
Maximum insulin-dependent glucose clearance (L/h) Adolescents		NA	NA	7.42 (22)	75	6.86 (3.84, 10.3)	65 (25-104)
Maximum insulin-dependent glucose clearance (L/h) Children		NA	NA	8.32 (24)	75	6.72 (2.70, 13.5)	65 (25-104)
Central volume of distribution (L)	θ6	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]
Peripheral volume of distribution (L)	θ7	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]
Intercompartmental clearance (L/h)	θ9	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]
Rate constant for glucose effect compartment (/h) (K_{LE})	θ10	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]
Formation of endogenous glucose during the meal period (mg)	θ16	4.79 (14)	7.1 *fix*[f]	1.34 (27)	7.1 *fix*[f]	1.27 (1.11, 1.45)	7.1 *fix*[f]
Concentration of insulin lispro giving 50% of maximum insulin-dependent glucose clearance (pmol/mL)	θ17	338 (9.4)	7.1 *fix*[f]	244 (2.8)	7.1 *fix*[f]	233 (194, 290)	7.1 *fix*[f]
Shape parameter for insulin lispro	θ18	1.86 (10.4)	7.1 *fix*[f]	21.3 (20)	7.1 *fix*[f]	22.5 (5.68,40.9)	7.1 *fix*[f]
Residual variability (%)	θ11	22 (1.4)		42 (1.8)		42 (39, 45)	

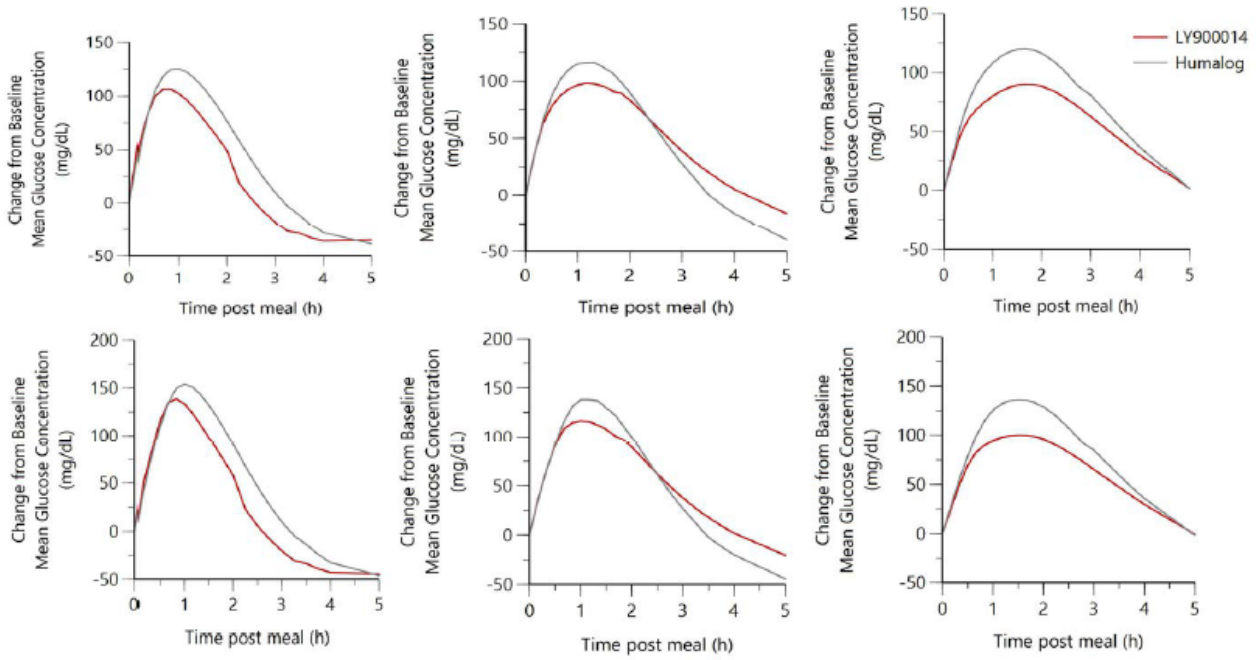
CI = confidence interval; **CSII** = continuous subcutaneous insulin infusion; **CV** = coefficient of variation; **IGI** = integrated insulin-glucose; **IIV** = interindividual variability; **%RSE** = relative standard error of the estimate as a percentage; **SAEM** = stochastic approximation expectation maximization; **T1DM** = type 1 diabetes mellitus.
a Fixed to value from Alskär et al. 2016.
b Fixed to value from Hovorka et al. 2004.
c Fixed to value from Silber et al. 2010.
d Fixed to value from Schneck et al. 2013.
e Fixed to value from CSII model (Lilly data on file).
f Fixed to facilitate efficient operation of the SAEM algorithm.
g Fixed to value from sensitivity analysis.

Simulations for paediatric and adult patients with T2D

The previously developed PK/PD model for adults with T2D (Study ITRW) was adjusted based on the changes made between the PK/PD model in adult patients with T1D and the final optimized PK/PD model

for adults, children, and adolescents with T1D in Study ITSA Part A. This paediatric/adult T2D PK/PD model was used to simulate glucose time course following a liquid MMTT when either LY900014 or Humalog was administered immediately prior or 20 minutes after the start of the test meal. The simulated PPG curves indicated less pronounced postprandial glucose excursion with LY900014 compared to Humalog (Figure 15).

Figure 15. Model-simulated change from baseline glucose concentration versus time from liquid MMTT following SC injection of a 0.2 U/kg dose of either LY900014 or Humalog when insulins are given immediately prior (top) and 20 minutes after (bottom) the start of the meal in children (left), adolescents (middle), and adults (right) with T2D.



PK/PD model: PPG after liquid test meal, Study ITSA, CSII

A PK/PD model for adults with T1D on CSII therapy (studies ITRF and ITSC) was previously developed but was not applicable for study ITSA Part B because the test meal in studies ITRF and ITSC was solid whereas liquid test meal was used in study ITSA. Therefore, PK/PD models following a liquid test meal developed for T1D patients on SC injections therapy (adults: study ITRV; adults and paediatric: study ITSA Part A) were utilized.

First, all IGI model parameters were fixed to estimates for adult T1D model from Study ITRV. The VPCs indicated that the model underpredicted the glucose concentrations observed in Study ITSA Part B. Next, all IGI model parameters were fixed to the estimates for the model optimized for study ITSA Part A. The VPCs indicated that the latter model better described the glucose concentrations observed in study ITSA Part B.

The parameter estimates for the final optimized model are provided in Table 16. The VPCs for the final PK/PD model for study ITSA Part B are shown in Figure 16.

Table 16. Parameter Estimates of the Optimized IGI Model for T1D (Study ITSA)

Model		Study ITSA (Part A): Children, Adolescents, and Adults with T1DM				Study ITSA (Part B): Children, Adolescents, and Adults with T1DM			
Parameter		Estimate (%RSE)	IIV (%CV)	Bootstrap Median (95% CI)	Bootstrap IIV (95% CI)	Estimate (%RSE)	IIV (%CV)	Bootstrap Median (95% CI)	Bootstrap IIV (95% CI)
Gastric emptying									
Emptying rate predose (/min) (KW_{pre})	Θ_{19}	0.0207 (7.6)	135 *fix*[g]	0.0200 (0.0086, 0.0306)	135 *fix*[g]	0.0207 *fix*[h]	135 *fix*[h]	NA	NA
Emptying rate postdose (/min) (KW_{post})	Θ_{20}	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]	0.167 *fix*[g]	135 *fix*[g]	NA	NA
Amount of glucose giving 50% of inhibition (cg) (DUO_{KM})	Θ_2	188 (8.3)	42 (14)	173 (147, 221)	47 (22, 66)	188 *fix*[h]	42 *fix*[h]	NA	NA
Shape parameter for glucose inhibition (GAMMA)	Θ_3	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]	14 *fix*[a]	7.1 *fix*[f]	NA	NA
Delay in emptying for the meal (min)	Θ_8	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]	0.0368 *fix*[e]	7.1 *fix*[f]	NA	NA
Glucose absorption									
Maximum rate of absorption from duodenum (cg/h)	Θ_{13}	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]	3480 *fix*[a]	7.1 *fix*[f]	NA	NA
Maximum rate of absorption from jejunum (cg/h)	Θ_{14}	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]	12400 *fix*[a]	7.1 *fix*[f]	NA	NA
Maximum rate of absorption from ileum (cg/h)	Θ_{15}	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]	7980 *fix*[a]	7.1 *fix*[f]	NA	NA
Amount of glucose giving 50% of maximum absorption (cg) (KM_{GLU})	Θ_{12}	127 (6.2)	7.1 *fix*[f]	112 (89.1, 154)	7.1 *fix*[f]	127 *fix*[h]	7.1 *fix*[f]	NA	NA
First pass effect on glucose	Θ_1	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]	0.80 *fix*[b]	7.1 *fix*[f]	NA	NA
Glucose disposition									
Insulin-independent glucose clearance (L/h)	Θ_4	1.89 *fix*[e]	59.3 *fix*[d]	1.89 *fix*[e]	59.3 *fix*[d]	1.89 *fix*[e]	59.3 *fix*[d]	NA	NA
Maximum insulin-dependent glucose clearance (L/h) Adult		11.4 (20)	75 (16)	11.7 (7.53, 15.0)	65 (25, 104)	9.16 (19)	62 (20)	9.00 (6.05, 12.1)	57 (39, 76)
Maximum insulin-dependent glucose clearance (L/h) Adolescents		7.42 (22)	75 (16)	6.86 (3.84, 10.3)	65 (25, 104)	6.44 (19)	62 (20)	6.45 (5.00, 7.87)	57 (39, 76)
Maximum insulin-dependent glucose clearance (L/h) Children		8.32 (24)	75 (16)	6.72 (2.70, 13.5)	65 (25, 104)	4.73 (26)	62 (20)	4.73 (1.03-8.62)	57 (39-76)
Central volume of distribution (L)	Θ_6	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]	9.33 *fix*[c]	7.1 *fix*[f]	NA	NA
Peripheral volume of distribution (L)	Θ_7	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]	8.56 *fix*[c]	7.1 *fix*[f]	NA	NA
Intercompartmental clearance (L/h)	Θ_9	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]	26.5 *fix*[c]	7.1 *fix*[f]	NA	NA
Rate constant for glucose effect compartment (/h) (K_{LE})	Θ_{10}	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]	2.1 *fix*[e]	7.1 *fix*[f]	NA	NA
Formation of endogenous glucose during the meal period (mg)	Θ_{16}	1.34 (27)	7.1 *fix*[f]	1.27 (1.11, 1.45)	7.1 *fix*[f]	1.34 *fix*[h]	7.1 *fix*[f]	NA	NA
Concentration of insulin lispro giving 50% of maximum insulin-dependent glucose clearance (pmol/mL)	Θ_{17}	244 (2.8)	7.1 *fix*[f]	233 (194, 290)	7.1 *fix*[f]	244 *fix*[h]	7.1 *fix*[f]	NA	NA
Shape parameter for insulin lispro	Θ_{18}	21.3 (20)	7.1 *fix*[f]	22.5 (5.68, 40.9)	7.1 *fix*[f]	21.3 *fix*[h]	7.1 *fix*[f]	NA	NA
Residual variability (%)	Θ_{11}	42 (1.8)		42 (39, 45)		42 *fix*[h]			

Abbreviations: CI = confidence interval; CV = coefficient of variation; IGI = integrated insulin-glucose; IIV = interindividual variability; MDI = multiple daily injection; NA = not applicable; %RSE = relative standard error of the estimate as a percentage; T1DM = type 1 diabetes mellitus.

[a] Fixed to value from Alskär et al. 2016.

[b] Fixed to value from Hovorka et al. 2004.

[c] Fixed to value from Silber et al. 2010.

[d] Fixed to value from Schneck et al. 2013.

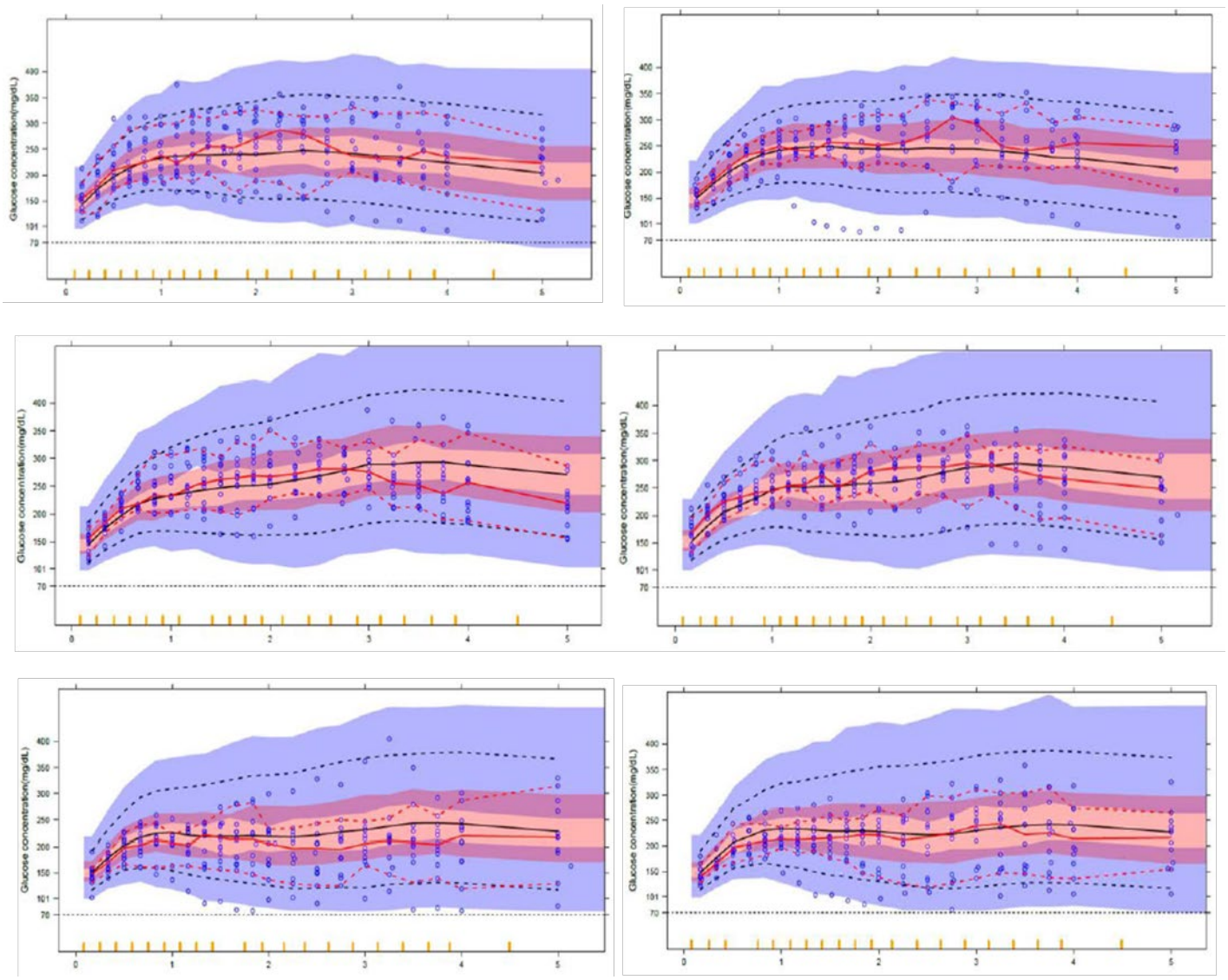
[e] Fixed to value from CSII model (Lilly data on file).

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

[g] Fixed to value from sensitivity analysis.

[h] Fixed to value from the pediatric/adult MDI IGI model.

Figure 16. VPC for the optimized paediatric/adult PK/PD model for Study ITSA Part B. Model predictions of glucose concentration during the liquid MMTT following administration of LY900014 (right) and Humalog (left) immediately prior to the start of the meal in children (top), adolescents (middle), and adults (bottom) with T1D.



2.3.5. Discussion on clinical pharmacology

Bioanalytics

The bioanalytical methods used in the clinical studies of LY900014 included in this submission have, in general, been appropriately described and validated according to relevant guidance. Most of the used analytical methods have been a part of previous (and/or the original) submissions.

In the clinical study ITSB included in this submission, the same radioligand binding assay used for the detection of anti-insulin lispro antibodies in human serum was implemented by 2 vendors: one intended for samples collected in the People's Republic of China (PRC) at WuXi AppTec (WaiGaoQiao Free Trade Zone, Shanghai, China), and the other intended for samples collected from patients outside the PRC at Eurofins (Saint Charles, MO, USA). The assay validation at Eurofins was part of the original MAA submission and has been discussed at the time.

An appropriate validation of the method at WuXi AppTec was provided in this submission. The validation covered relevant parameters and the method at WuXi AppTec can be considered acceptable for the intended purpose. It seems that no actual comparability evaluation of assay performance was performed by e.g. analysis of the same samples at both facilities, however, comparison of key validation parameters at WuXi AppTec (new vendor) and at Eurofins (old vendor) indicates that the RBA assay performs similarly at both facilities.

Observed PK and PD in paediatric patients

PK and PD data were collected in a limited number (n = 12 to 14) of children (8 to 11 years) and adolescents (12 to 17 years) with T1D following a single SC injection and CSII bolus infusion in study ITSA Part A and Part B, respectively. In the phase 3 study ITSB, it was not feasible to collect PK data due to rapid elimination of insulin lispro.

Overall, the PK data from study ITSA and prior studies in adults demonstrate that following a SC injection, the early insulin lispro exposure parameters (e.g. AUC[0-30min], AUC[0-1h]) were higher with LY900014 compared to Humalog, indicating faster absorption, and the total exposure (AUC[0-inf]) was comparable. There appeared to be lower early PPG excursion with LY900014 compared to Humalog when insulin lispro was administered for children and adolescents as SC injection with significant reductions in PPG response over 2 hrs (BGΔAUC[0-2h]) in children and adolescents, but no statistically significant difference between the study drugs was demonstrated over the complete 5-hour test meal period in study ITSA Part A.

Following a CSII bolus infusion administrated via insulin pump (ITSA Part B), the very early exposure parameters (AUC[0-15min] AUC[0-30min]) suggested slightly faster absorption with LY900014 compared to Humalog in children, adolescents and adults, but the differences were not statistically significant for the primary PK endpoints. The PPG excursions following a liquid test meal and CSII bolus infusion were similar for LY900014 and Humalog in children, adolescents, and adults. It is difficult to compare the results for different studies using CSII bolus infusion (i.e. ITSA Part B and prior studies in adults), because different insulin doses and infusion rates and test meals were used in the studies.

PK and PK/PD modelling

The population PK and PK/PD modelling conducted by the MAH are considered supplementary information for the current application; Refer to section 3 Benefit-Risk Balance of this AR. Main issues related to the models are briefly presented below, but no questions are raised on issues related to PK and PK/PD models. Overall, the submitted modelling reports for paediatric and adult patients in study ITSA were cursory compared with the prior models for studies conducted in adults.

Population PK models

The first insulin lispro population PK model was for administration via IV and SC injection. The model was based on 8 clinical pharmacology studies with frequent sampling and a total of 338 adult subjects. Model development started with establishing a 3-compartment disposition model with clearance from the central compartment. The disposition model was based on data observed after IV injection and the parameter estimates were fixed in the subsequent models. Next, absorption model (a mixed zero- and first-order absorption) following SC injection of LY900014 was added and, subsequently, the effects of treatment (LY900014 vs Humalog) and population differences (patients with T1D vs T2D vs healthy) were assessed on the absorption of insulin lispro. Finally, it was estimated that subjects with anti-insulin lispro antibodies (ADA) had increased insulin lispro clearance (+16.5%); this effect was statistically significant. However, the effect of ADA on insulin lispro kinetics was not included in the final model. The MAH's grounds for this decision were that because insulins are individually dosed, the change in clearance was not expected to produce clinically meaningful difference in glycaemic control.

The prior adult PPK model for SC injection overpredicted the insulin lispro concentrations in the elimination phase for children and adolescents from study ITSA Part A. Surprisingly, it was not shown whether the prior adult PPK model was able to characterize the PK in adults from study ITSA Part A. Importantly, in study ITSA Part A the proportion of ADA positive subjects was very high [13/13 (100%) in children, 13/14 (92.9%) in adolescents, and 12/15 (80%) in adults] compared with the proportion of ADA+ subjects in the prior adult dataset (24%). Some model parameters were re-estimated, which improved the fit to some extent. At present, the MAH has one PPK model for SC injection in adults based on relatively large dataset (the prior model) and another for adults and paediatric patients (8 to 17 years) based on a relatively small dataset (ITSA Part A). It would be preferable to have a joint model.

A population PK model for CSII bolus infusion was developed by utilizing the prior 3-compartment disposition model and estimating the absorption kinetics with data from adult studies ITRF and ITSC. The VPC plots indicated that the model overpredicted insulin lispro concentrations for adults in study ITSA Part B during the very early absorption phase as well as at the elimination phase. It seems that for the CSII model it was appropriate to re-estimate at least some absorption parameters. This may be attributed to the prolonged duration of administration with CSII. For SC injections, the dose will always be administered over a few seconds. Furthermore, the cannula of an insulin pump is more complex than a SC needle, which might add further differences between studies in which different insulin pumps may have been used. It is known that the dwelling time of the insulin pump cannula has significant effect on the absorption kinetics. As with SC injection, the MAH presently has two population PK models for CSII bolus infusion based on different datasets. It would be preferable to have a joint model, but this may be more difficult to achieve for CSII administration.

PK/PD models

A sequential PK/PD modelling approach was used to analyze the postprandial glucose response after a test meal. The relationship between LY900014 and Humalog administration, insulin concentrations in serum predicted by a population PK model, and the corresponding effect on glucose concentrations was evaluated using an exposure-response model that utilized a mechanistic Integrated Glucose-Insulin (IGI) model.

A PK/PD model was initially developed for adult T1D patients with data from study ITRV (SC injection, liquid test meal). Interestingly, it seems that the effect of insulin on endogenous glucose production was not included in the IGI model for T1D patients whereas it was included for T2D patients. The rationale for this was not discussed in the modelling report. This model failed to predict postprandial glucose levels in a new population (adults from study ITSA Part A). It was necessary to re-estimate several parameters characterizing gastric emptying, glucose absorption and glucose disposition to achieve a model that was able to characterize the glucose response observed in study ITSA Part A.

Overall, the presented modelling exercises in adult and paediatric patients to characterize the exposure-response relationship between insulin lispro concentration and postprandial glucose response highlight the several challenges of the task. Even in adult patients with T1D, the PK/PD model developed in one population (study ITRV) failed to characterize the postprandial glucose excursion in another population (study ITSA Part A). Extrapolation of the insulin-glucose PK/PD model for study ITSA Part A to patients with T2D is expected to be very challenging and the presented simulations should be interpreted very cautiously.

2.3.6. Conclusions on clinical pharmacology

Observed PK data in study ITSA indicate that following a single SC injection, the early absorption of insulin lispro was faster with LY900014 compared to Humalog in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years). No significant differences between LY900014 and Humalog were observed in terms of total exposure, peak concentration (Cmax) and time to peak concentration (tmax). Following a single bolus infusion via CSII pump, a trend towards an accelerated

absorption of insulin lispro was observed with LY900014 compared to Humalog. Overall, pharmacokinetic differences between LY900014 and Humalog appeared to be lesser following CSII bolus infusion compared with differences observed following SC injection.

Evaluation of glucose excursion following a liquid mixed meal and a single dose of LY900014 and Humalog given immediately before the start of the meal was a secondary objective of study ITSA. The results indicated no compelling difference in the overall postprandial glucose excursion between LY900014 and Humalog in children and adolescents when given immediately before a meal, although the early increase in blood glucose might be attenuated with SC injection of LY900014. Because a liquid test meal and fixed insulin dose of 0.2 U/kg (in contrast to individually adjusted dose) were used in study ITSA, it is difficult to estimate the clinical significance of these results.

The population PK and PK/PD modelling and simulation exercises conducted by the MAH are acknowledged. Further development of the PK models is encouraged, especially it is advised to include the effect of anti-drug antibodies in the models. The presented PK/PD models highlight the challenges of modelling postprandial glycaemia and extrapolation of models to new populations. Overall, the PK and PK/PD models are considered supplementary information for the benefit-risk (B/R) assessment of the current variation application and, therefore, no questions are raised on the models.

2.4. Clinical efficacy

2.4.1. Main studies

The paediatric development program of Lyumjev (LY900014) includes 2 clinical studies in which LY900014 was administered to paediatric patients with T1D.

1. A clinical pharmacology study ITSA, which established the PK and glucodynamic profile during a test meal of LY900014 and Humalog following a single SC bolus dose administered through injection or CSII in paediatric and adult patients with T1D. Under Article 46, Study ITSA was previously reviewed (EMEA/H/C/005037/II/0005). Additional analyses from study ITSA submitted with this variation are assessed in section 2.3 of this AR.
2. I8B-MC-ITSB / A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes: PRONTO-Peds. In this AR, the study is referred to as ITSB.

The evaluation of efficacy and safety of LY900014 in children and adolescents aged from 1 year to <18 years is in this procedure based on the ITSB.

PK modelling reports (MDI Pop PK Report Addendum: Study ITSA Part A; CSII Pop PK Report Addendum: Study ITSA Part B; Pop PK ITRF-ITSC) included in the current submission are assessed in Sections 2.3.2 to 2.3.6 of this AR.

2.4.1.1. Methods

2.4.1.1.1. Study design

Study ITSB was a Phase 3 study designed to evaluate LY900014 compared to Humalog in combination with basal insulin in children and adolescent patients with T1D.

The study consisted of 3 treatment groups:

- LY900014, given 0 to 2 minutes prior to the meal

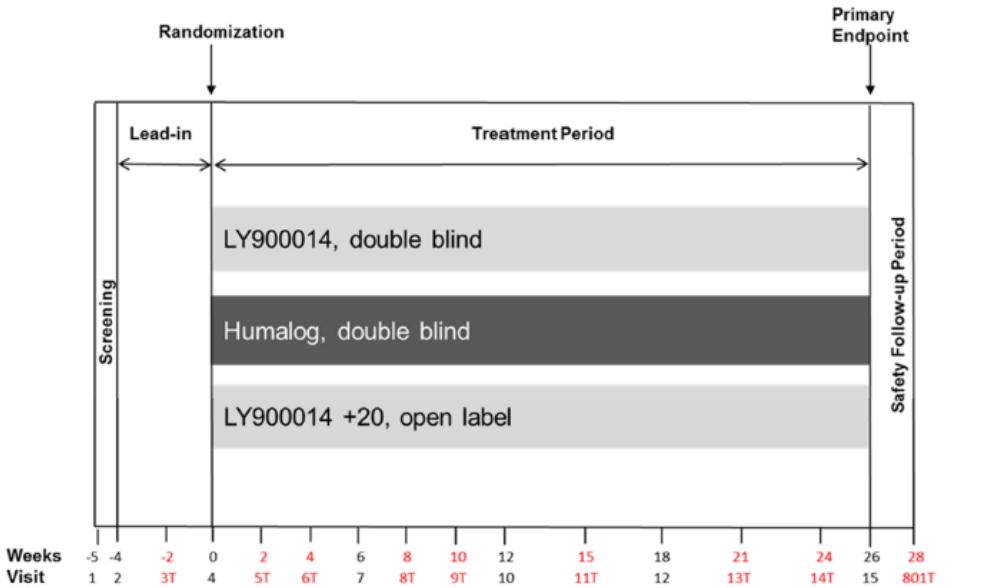
- Humalog, given 0 to 2 minutes prior to the meal, or
- LY900014+ 20, given up to 20 minutes after the start of a meal.

The study was designed to demonstrate noninferiority of LY900014 compared with Humalog in change from baseline to Week 26 in HbA1c when injected 0 to 2 minutes prior to the start of the meal, comparing treatment groups 1 and 2 on the list above. The third treatment group was open label due to inability to blind postprandial injection timing of LY900014 and evaluated the efficacy and safety of postprandial dosing, which often occurs in children due to unpredictable eating patterns and activity. (Figure 17).

The study consisted of 4 periods:

- 1-week screening
- 4-week lead-in period
- 26-week treatment period, and
- 2-week safety follow-up period.

Figure 17 Illustration of study design.



Notes: Study visits in red text and "T" = telephone visits. LY900014 +20 = LY dose given up to 20 minutes after the start of the meal. Double-blind arms = dose given 0 to 2 minutes prior to the start of the meal.

During 4-week lead-in period, patients taking insulin aspart, insulin glulisine, faster insulin aspart, or biosimilar insulin lispro at screening switched to marketed insulin lispro (Humalog) while remaining on their basal insulin regimen (insulin glargine, insulin detemir, or insulin degludec) throughout the study. Glucose target values were recommended and were used to determine insulin dose titration by the investigator. During the lead-in, emphasis was on basal insulin adjustment. Prandial insulin was titrated to achieve optimal dosing during the first 12 weeks. Therefore, the primary endpoint HbA1c reflected glucose control during the 3-month time period when there were minimal changes. Adjustment of basal and prandial insulin doses was allowed throughout the treatment period to achieve or maintain glycaemic targets or for safety reasons.

Glucose monitoring

Patients were required to collect glucose values at least 4 times (before meals and bedtime) each day using the BG meter provided or a personal CGM/FGM that is approved for nonadjunctive use; i.e. results could

be used to make insulin dosing decisions per their local country regulations. The investigator reviewed glucose values at office and telephone visits in order to determine any insulin dose adjustments. Once BG targets were achieved and basal and prandial dose titration had been optimised, daily 4-point glucose testing frequency and timing could be adjusted at the investigator's discretion in consultation with patient and caregiver.

2.4.1.1.2. Study participants

Inclusion/Exclusion Criteria

Participants were eligible if they

- had T1D diagnosed by an endocrinologist, diabetes specialist, or physician for at least 6 months
- were at least 1 to <18 years of age
- were ≥16 lbs. (7.3 kg)
- had been treated with only 1 of the following rapid-acting insulin analogs as part of an MDI regimen for at least the last 90 days:
    - insulin lispro U-100
    - insulin aspart U-100
    - insulin glulisine U-100, or
    - fast acting insulin aspart
- had been treated with only 1 of the following basal insulins for at least the last 90 days:
    - insulin glargine U-100 (QD or BID)
    - insulin detemir U-100 (QD or BID), or
    - insulin degludec U-100 (QD)
- used a total daily dose of insulin 0.3 to ≤1.9 U/kg
- had an HbA1c value ≤9.9% according to the central laboratory
- Male patients: no male contraception required, except in compliance with specific local government regulations
- Female patients of childbearing potential:
    - Post pubertal females of childbearing potential are defined as children and adolescents ≥12 years of age or <12 years of age who have onset of menses.
    - if sexually active, must agree to use 1 highly effective form of contraception for the entirety of the study
    - not pregnant or intending to become pregnant
        - post pubertal females of childbearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure to investigational product (IP) at Visit 4
    - not breastfeeding

Participants were ineligible if they had

- current hypoglycaemic unawareness in the investigator's opinion or have had more than 1 episode of severe hypoglycaemia within 6 months prior to screening (Visit 1)
- more than 1 emergency room visit or hospitalization due to poor glucose control (hyperglycaemia or DKA) within 6 months prior to screening (Visit 1)
- any other clinically significant disorder or uncontrolled concomitant disease that, in the investigator's opinion, would preclude participation in the trial or pose a safety risk
- Renal:
    - history of renal transplantation,

    - currently receiving dialysis, or
    - have a history of renal impairment (exclusion only if glomerular filtration rate [estimated GFR] <60 mL/minute/1.73 m2 as defined by the central laboratory.
- obvious clinical signs or symptoms of liver disease in the opinion of the investigator (for example, acute or chronic hepatitis or cirrhosis) or elevated liver enzyme measurements as indicated below at screening:
    - total bilirubin ≥2× the upper limit of normal (ULN) (with the exception of Gilbert's disease) as defined by the central laboratory, or
    - alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≥3×ULN as defined by the central laboratory, or
    - aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase ≥3×ULN as defined by the central laboratory
- Active or untreated malignancy or in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years
- Known hypersensitivity or allergy to any of the study insulins or their excipients
- Blood transfusion or severe blood loss within 3 months prior to Visit 1 or have known hemoglobinopathy, anaemia, haemolytic anaemia, sickle cell anaemia, or any other traits of haemoglobin abnormalities known to interfere with the HbA1c measurement
- History of inpatient psychiatric treatment; emotional, behavioural, or other untreated conditions that, in the opinion of the investigator, would interfere with proper participation in routine diabetes control and management in the last 6 months
- significant lipohypertrophy
- Retinopathy and maculopathy: have pre-proliferative and proliferative retinopathy, or maculopathy requiring treatment or not clinically stable in the last 6 months, or patients with active changes in subjective eye symptoms as determined by the investigator if an eye exam has not been performed in the last 6 months.
- Receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, and inhaled preparations) or have received such therapy within the last 90 days.
- been on a treatment regimen that included regular human insulin, neutral protamine Hagedorn, Afrezza® (insulin human) inhalation powder, any premixed insulins, or use of diluted insulins within the last 90 days
- received any oral or injectable medication intended for the treatment of diabetes mellitus other than insulins within the last 90 days, or been treated by CSII regimen for ≥14 days within the last 90 days
- Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged by the investigator to not to be scientifically or medically compatible with this study.

Subjects were excluded if the patient or caregiver were investigator site personnel directly affiliated with this study or a member of their immediate families; or if the patient or caregiver was an immediate family member of Lilly employees.

2.4.1.1.3. Treatments

Table 17 outlines the study interventions.

Table 17 Study interventions administered

Regimen	Dose Strength	Dose Administration	Route of Administration	Timing of Administration
LY900014	100 U/mL	Individualized dosing	Subcutaneous	0 to 2 minutes before start of the meal
Humalog	100 U/mL	Individualized dosing	Subcutaneous	0 to 2 minutes before start of the meal
LY900014+20	100 U/mL	Individualized dosing	Subcutaneous	Up to 20 minutes after the start of the meal

The glucose target values shown in Table 18 are suggested guidelines that are required in order to achieve an HbA1c goal of <7.0% (53 mmol/mol) and could be used to determine insulin dose titration. Targets could be individualised, aiming for the lowest achievable HbA1c without undue exposure to severe hypoglycaemia. A higher HbA1c goal (in most cases <7.5% (58 mmol/mol) could be appropriate in younger children who are unable to articulate symptoms of hypoglycaemia.

Table 18 Glucose Target Values

	Target Range
Before meals	70 - 130 mg/dL (4.0-7.0 mmol/L)
Postprandial (1 hr)	90 to 180 mg/dL (5.0 to 10.0 mmol/L)
Bedtime	80-140 mg/dL (4.4-7.8 mmol/L)
HbA1c	<7.0% (53 mmol/mol)

Abbreviations: HbA1c = hemoglobin A1c; w/out = without.

In the blinded treatment groups, LY900014 and Humalog was administered immediately prior to each meal (0–2 minutes). The LY900014+20 open label treatment group administered the dose up to 20 minutes after the start of a meal.

The patient's basal insulin during the study could be dosed at any time and was to be taken at approximately the same time each day. Patients were required to use the same basal insulin regimen (type and dosing frequency) throughout the study.

Detailed advice regarding adjustment of prandial and basal insulin were included in the protocol (not copied in this AR for brevity). The prescribed prandial insulin dose was determined by, and the responsibility of, the investigator in consultation with the patient or caregiver. Patients were to attempt to eat 3 meals (morning, mid-day, and evening) with at least 3 doses of meal-related IP every day. Patients could also eat a snack and inject insulin to cover the carbohydrates eaten if that was their usual practice. Patients were to administer IP to correct high BG using their usual method for determining a correction dose

2.4.1.1.4. Objectives

Table 19 shows the objectives and endpoints of the study.

The primary objective of the study was to test the hypothesis that LY900014 is noninferior to Humalog on glycaemic control, measured by the change from baseline in HbA1c in patients 1 to <18 years of age with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin for 26 weeks.

It is to be observed that the non-inferiority margin of 0.4% in the table is for the FDA, for the EU then non-inferiority margin (NIM) is 0.3% (3 mmol/mol). The protocol (version B) states:*" For both primary analysis approaches, LY900014 will be declared noninferior to Humalog if the upper limit of the 2-sided 95%*

confidence interval (CI) for the least-squares (LS) mean difference in the change from baseline in HbA1c for LY900014 minus Humalog is below +0.4%. In addition, the 95% CI for the treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05." The MAH states in the Summary of Clinical Efficacy that A NIM of 0.4% has been developed consistent with the FDA guidelines. The primary endpoint was also assessed using a NIM of 0.3%, in line 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). For further justification of the NIM, see section 2.4.1.1.10.

Table 19 Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
1. To test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (NIM=0.4% for HbA1c) in patients 1 to <18 years of age with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal) in combination with basal insulin as part of a multiple daily injection regimen for 26 weeks	1. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Gated Objectives	
2. To test the hypothesis that LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal (LY900014+20) is noninferior to Humalog, administered as prandial insulin (0 to 2 minutes prior to the meal), on glycemic control (NIM=0.4% for HbA1c)	2. Change from baseline to Week 26 in HbA1c
3. To test the hypothesis that LY900014 is superior to Humalog in improving glycemic control (HbA1c) when administered as prandial insulin (0 to 2 minutes prior to the meal)	3. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
4. To compare LY900014, LY900014+20, and Humalog with respect to the incidence and rate of documented post-dose hypoglycemia	4. Rate (events/patient/year) and incidence (percentage of patients with events) of documented post-dose hypoglycemic events within 1 and 2 hours after the prandial dose from Weeks 0 through Week 26
5. To compare LY900014, LY900014+20, and Humalog with respect to the incidence and rate of documented hypoglycemia	5. Rate (events/patient/year) and incidence (percent of patients with events) of documented hypoglycemic events from Week 0 through Week 26
6. To compare LY900014, LY900014+20, and Humalog on the rate of severe hypoglycemic events	6. Rate (events/patient/100 years) of severe hypoglycemic events from Weeks 0 through 26
7. To compare LY900014, LY900014+20, and Humalog with respect to total, basal, and prandial insulin dose	7. Change from baseline in total, basal, and prandial insulin doses and prandial/total insulin dose ratios at Week 26
8. To compare LY900014, LY900014+20, and Humalog with respect to the proportion of patients achieving HbA1c targets	8. The proportion of patients with HbA1c <7% and <7.5% at Week 26
9. To compare LY900014, LY900014+20, and Humalog with respect to 7-point SMBG	9. Change from baseline to Week 26 in 7-point SMBG values
Tertiary/Exploratory Objectives	
10. To compare LY900014, LY900014+20, and Humalog with respect to changes in body weight	10. Change in weight (kg) from baseline to Week 26
11. To compare LY900014, LY900014+20, and Humalog with respect to glycemic variability	11. Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 7-point SMBG profiles
12. To compare the incidence of treatment-emergent anti-insulin lispro antibodies for LY900014, LY900014+20, and Humalog	12. Incidence of treatment-emergent anti-insulin lispro antibodies

Abbreviations: HbA1c = hemoglobin A1c; NIM = noninferiority margin; SMBG = self-monitored blood glucose; T1D = type 1 diabetes.

2.4.1.1.5. Outcomes/endpoints

Primary Efficacy Assessment

The primary efficacy measure was the change from baseline to Week 26 in HbA1c.

Secondary Efficacy and Safety Assessments

The following secondary efficacy measures were collected at the times shown in the Schedule of Activities (Table 20).

- Prandial, basal, and total insulin doses (units and units/kg) and prandial/total insulin ratio
- Proportion of patients with HbA1c<7.0% and <7.5%
- self-monitored blood glucose (SMBG) 7-point profiles (fasting, 1-hour post morning meal, pre midday meal, 1-hour post midday meal, pre evening meal, 1 hour post evening meal, and bedtime)
    - 1-hour PPG excursions
    - within- and between-day glucose variability measured by the coefficient of variation and standard deviation (SD).

Safety Assessments

- Rate and incidence of hypoglycaemia:
    - documented post-dose
    - documented
    - severe
- Adverse events
- Laboratory value assessments
- Weight

Table 20 Schedule of Activities

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

Table 21 Schedule of Activities (continued)

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[a] [b]
eCRF Visit Number	1	2	3[b,c]	4	5[b,c]	6[b,c]	7	8[c,b]	9[b,c]	10	11[b,c]	12	13[b,c]	14[b,c]	15	801[c,d]	ED
Weeks from Randomization	−5	−4	-2	0	2	4	6	8	10	12	15	18	21	24	26	28	
Visit Window (±days)		3	3	3	7	7	7	7	7	7	7	7	7	7	7	7	
Ancillary Supplies/Diaries/IP																	
Dispense blood glucose meter and ancillary supplies and complete training[j,k,l]		X		X			X			X		X					
Diabetes education and nutrition counseling[k,l]		X															
Dispense study diaries and complete training[k,l]		X		X			X			X		X					
Collect study diaries				X			X			X		X			X		X
Dispense IP		X		X			X			X		X					
Train on collecting 4- and 7-point SMBG profiles[l,m]		X															
Laboratory Assessments																	
Pregnancy test, serum/urine (applicable females only)[m,n]	X			X													

[a] Patients who rescreen will start at Visit 1.

The definitions of efficacy and safety analyses used in the study are provided in Table 22.

Table 22 Baseline and Postbaseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Postbaseline Observations
Lead-in Period			
HbA1c ANCOVA	All Randomized Patients	Visit 1	Visit 4 prior to initiation of IP
Basal, bolus, and total insulin doses, and bolus/total insulin dose ratios continuous analysis	All Randomized Patients	Not applicable	Visits 3 and 4
TEAE	All Enrolled Patients	Prior to first dose of open-label insulin lispro (or Visit 2 date if the dose date is missing)	The entire lead-in period after first dose of open-label insulin lispro and prior to the first dose of IP (or Visit 4 if the dose date is missing)
26-Week Treatment Period (including Safety Follow-up Visit where applicable)			
HbA1c ANCOVA (ITT estimand)	All Randomized Patients	Last of Visits 1-4	Visit 15 with imputation for patients who discontinue study prior to Visit 15
HbA1c MMRM (efficacy estimand)	All Randomized Patients with a baseline and at least 1 postbaseline observation while on IP	Last of Visits 1-4	Visits 7, 10, and 15 prior to discontinuation of IP
HbA1c categorical analysis longitudinal logistic regression	All Randomized Patients with a baseline and at least 1 postbaseline observation while on IP	Last of Visits 1-4	Visits 7, 10, and 15 prior to discontinuation of IP
CGM outcomes	All Randomized Patients with at least 1 from baseline and postbaseline observations	Visit 4	Visit 15
Basal, bolus, and total insulin doses, and bolus/total insulin dose ratios continuous analysis	All Randomized Patients	Last of Visits 3-4	Visits 5-15 prior to discontinuation of IP
7-point SMBG	All Randomized Patients with a baseline and at least 1 postbaseline observation	Visit 4 prior to initiation of IP	Visits 10 and 15 prior to discontinuation of IP
Health outcomes (PedsQL)	All Randomized Patients with a baseline and a postbaseline observation	Visit 4	Visits 15 prior to discontinuation of IP
Safety laboratory tests (chemistry, hematology) – continuous analysis	All Patients in the Safety Population with a baseline and a postbaseline observation	Last of Visits 1-4	Last of Visits 5-15 (planned including early discontinuation visits) regardless of IP use
Safety laboratory tests (chemistry, hematology) – categorical analysis	All Patients in the Safety Population with a normal baseline (with respect to the direction being analyzed) and a postbaseline observation	Last of Visits 1-4	Visits 5-15 (including unplanned visits) regardless of IP use
Hypoglycemic events	Safety Population	All Visits 2-4	All Visits 5-15 prior to discontinuation of IP
Weight and vital signs	All Patients in the Safety Population with a baseline and a postbaseline observation	Last of Visits 1-4	Visits 7, 10, 12, and 15 prior to discontinuation of IP
Anti-insulin lispro antibodies	Safety Population	Visit 1	Visits 4, 7, 10, and 15 regardless of IP use
TEAE	Safety Population	Prior to first dose of randomized IP (or Visit 4 date if missing), after first dose of open-label Humalog (or Visit 2 date if missing)	From randomization to Week 26 prior to discontinuation of IP OR from randomization to safety follow-up

Abbreviations: ANCOVA = analysis of covariance; CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c; IP = investigational product; ITT = intention-to-treat; MMRM = mixed-effects model for repeated measures; PedsQL = Pediatric Quality-of-Life; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event.

2.4.1.1.6. Sample size

Approximately 708 patients were to be randomized in order that 600 patients complete the study through the primary endpoint at Week 26. Patients will be randomized in a 2:2:1 ratio to double-blind prandial LY900014 (LY900014) , Humalog, or open-label post-prandial LY900014 (LY900014+20).

Assuming a NIM of 0.4%, no true difference between treatment groups and a SD of 1.1%, 240 completers for each double-blind treatment group would provide greater than 95% power to show noninferiority between LY900014 and Humalog using the upper limit of a 2-sided 95% CI. This sample size was also estimated to provide more than 80% power to show noninferiority between LY900014 and Humalog using a 0.3% NIM at 26 weeks.

Additionally, with the assumption a difference no larger than 0.07% between treatment groups and a SD of 1.1%, 240 completers of Humalog and 120 completers of LY900014+20 would provide approximately 76% power to show noninferiority between LY900014+20 and Humalog using a NIM of 0.4%.

Assuming a 15% dropout rate during 26 weeks of treatment, approximately 708 patients (283 patients in each double-blind treatment group and 142 patients in the open-label treatment group) were to be randomised.

2.4.1.1.7. Randomisation and treatment assignment

Eligible patients were randomised to double-blind treatment or open label treatment at Visit 4. Assignment to treatment groups was be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

Patients were randomized to double-blind LY900014, double-blind Humalog, or open-label LY900014+20 in a 2:2:1 ratio. Stratification was by country, HbA1c stratum (≤8.0%, >8.0%) based on HbA1c measured at Visit 1, type of basal insulin at randomization (insulin glargine, detemir, or degludec), and age group (1 to <12, 12 to <18 years).

The IWRS was used to assign all IP (blinded and open-label) during the study.

2.4.1.1.8. Blinding (masking)

Study ITSB was a double-blind study; both treatment groups, LY900014 and Humalog, were administered immediately prior to each meal in a double-blind manner. Investigators, patients, and study site personnel were blinded to assigned insulin regimen throughout the study. The third treatment group consisting of LY900014 administered up to 20 minutes after the start of a meal (LY900014+20) was open-label, as blinding for this group was not possible. The sponsor remained blinded throughout the study for all treatment groups.

2.4.1.1.9. Analysis populations

Definitions of populations are given in Table 23.

The efficacy analysis was conducted on the Randomized Population, unless otherwise noted. The primary endpoint was also analysed using the Per Protocol Population and Completer Population.

Efficacy analyses for other secondary objectives and exploratory objectives were performed for the efficacy estimand.

Safety analyses were conducted on the Safety Population.

Analyses of AEs included 2 sets of analyses:

- data collected prior to permanent discontinuation of IP, and
- all data collected during the course of the entire study, including the follow-up visit, regardless of IP use.

Analyses of hypoglycaemia used data collected prior to permanent discontinuation of IP, while analyses for posttreatment was performed as needed.

Analyses of safety laboratory measurements was performed on all data during the planned treatment period regardless of IP use.

Table 23. Patient populations

Population	Description
Entered	All patients who sign informed consent.
Enrolled	All patients who receive at least 1 dose of open-label Humalog during the lead-in period
Randomized	All patients who are randomly assigned to study treatment at Visit 4. Treatment group will be defined on the basis of the treatment the patients are assigned.
Safety	All randomized patients who receive at least 1 dose of the randomly assigned IP. Treatment group will be defined on the basis of the treatment the patients are assigned.
Completer	Patients included in the Randomized Population who have completed Week 26 of study treatment without permanent discontinuation of IP. Treatment group will be defined on the basis of the treatment the patients are assigned.
Per Protocol	Patients included in the Randomized Population who have completed Week 26 of study treatment without permanent discontinuation of IP and without significant protocol deviations through Week 26 that would significantly impact the primary objective. Treatment group will be defined on the basis of the treatment the patients actually receive.
PedsQL	A subset of the Randomized Population who have an informed consent for the PedsQL addendum signed by parent(s)/legal guardian(s) and questionnaires completed at both baseline and postbaseline.
CGM	A subset of the Randomized Population who have an informed consent for CGM addendum signed by parent(s)/legal guardian(s) and valid CGM data at baseline or postbaseline. The CGM subgroup analysis is contained within a separate report.

Abbreviations: CGM = continuous glucose monitoring; IP = investigational product; PedsQL = Pediatric Quality-of-Life.

Note: The health outcome measure PedsQL was performed on 105 subjects in English speaking countries. This measure is not in the main protocol. However, the MAH submitted upon request the addendum of study ITSB, which includes the health outcome measure PedsQL**.**

2.4.1.1.10. Statistical methods

Analyses of primary objective

The clinical variable analysed for the primary objective, to show that LY900014 is noninferior to Humalog on glycaemic control, was change from baseline in HbA1c (%) at Week 26. Two alternative NIMs 0.3% and 0.4% were to be considered.

Efficacy estimand

For the EMA jurisdiction the primary estimand was set to be the "efficacy estimand" that included data collected prior to permanent discontinuation of IP.

The analysis model for the efficacy estimand was a MMRM, and thus in practise only patients with both baseline and at least 1 postbaseline values were included. The MMRM analysis model for the efficacy estimand included the fixed effects of treatment, the main effects of the stratification factors (type of basal insulin, age group [to <12 years, 12 to <18 years], and country), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. Countries in similar geographic regions with fewer than 10 patients were pooled to achieve a pooled country of at least 10 patients. Within-patient association matrix was assumed to be unstructured. LY900014 was to be declared noninferior to Humalog if the upper limit of the 2-sided 95% CI for the LS mean difference in the change from baseline in HbA1c for LY900014 minus Humalog was below +0.4%. In addition, the 95% CI for the treatment difference was compared to an alternative NIM of +0.3%.

ITT estimand

The other estimand defined, the "ITT estimand", included all data collected regardless of IP use. All patients with baseline value were included in the analysis.

For the ITT estimand, the multiple imputation method of return to baseline was used: The missing HbA1c measurement at Week 26 was imputed by the patient-level observed baseline value plus a noise for uncertainty, assuming a washout of any potential treatment effect. The noise followed a normal distribution with the variability estimated from the "washout HbA1c data", derived by subtracting the corresponding treatment mean at Week 26 from individual nonmissing HbA1c values at Week 26. (Of note: The copy reference method, originally planned as the first option, was not used because there were a limited number of patients who discontinued study drug before Week 26 but provided data at Week 26, i.e. the relevant reference group, and hence a limited dataset that could have been used for imputation with the copy reference approach.)

For the ITT estimand, an ANCOVA was used for each of the multiple imputed datasets with fixed effects of treatment and the main effects of the stratification factors (type of basal insulin, age group, and country [pooled]) as fixed effects and baseline HbA1c as a covariate, and model based mean difference calculated for the treatment groups. The final estimates were combined from at least 1000 imputations. LY900014 was to be declared noninferior to Humalog if the upper limit of the 2-sided 95% CI for the LS mean difference in the change from baseline in HbA1c for LY900014 minus Humalog was below +0.4%. In addition, the 95% CI for the treatment difference was compared to an alternative NIM of +0.3%.

Additional analyses of the primary objective

Additional analyses of HbA1c were completed for the primary variable: an MMRM model using the completer and per-protocol populations. Sensitivity analyses were conducted using a progressive stress test, implemented as tipping point analysis, for both efficacy and ITT estimands: The basic idea was to impute the missing values and add a value (delta) to the imputed values to find the delta value that would overturn the conclusion. If the delta required to overturn the primary result was not a plausible departure from what would be expected under missing-at-random assumption, then the primary result was considered robust to plausible departures from MAR.

A secondary analysis model for the efficacy estimand was an ANCOVA, using the model with strata (pooled country, type of basal insulin, and age group) and treatment as fixed effects and baseline as a covariate. Missing endpoints were imputed using the LOCF approach using postbaseline data only.

Justification for noninferiority margin

A NIM of 0.4% from both statistical and clinical perspectives was developed consistent with the Food and Drug Administration (FDA) guidelines. The primary endpoint was also assessed using a NIM of 0.3%, which is generally considered acceptable per the CHMP Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus.

The International Council for Harmonisation E10 states that the NIM cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared to placebo in the setting of the planned trial. The FDA "Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention" 2008 draft, which was in place at the time the study was conducted, states that a NIM of either 0.3% or 0.4% is acceptable in diabetes trials, provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in the previous placebo-controlled trials.

A NIM of 0.4% was also considered appropriate from the perspective of clinical relevance. Basing the clinical relevance upon the curvilinear relationship between HbA1c and microvascular complications and hypoglycaemia rates from the Diabetes Control and Complications Trial, the mean change in HbA1c represented by a NIM of 0.4% HbA1c would represent negligible increased rates of complications per 100 patient-years for patients with diabetes having a mean HbA1c of 8% at baseline (DCCT 1993; DCCT 1996).

Analyses of Multiplicity-Controlled Objectives

The analysis methods described above for the efficacy and ITT estimands were to be used for testing the two multiplicity-controlled secondary hypotheses: (1) whether LY900014+20 is noninferior to Humalog for glycaemic control, and (2) whether LY900014 was statistically superior to Humalog for glycaemic control. The two hypotheses above were to be tested hierarchically at two-sided 5% alpha level, provided the noninferiority of LY900014 to Humalog in glycaemic control is demonstrated first. (Of note: Although a simple hierarchical hypothesis test procedure was used, the MAH refers to it as being 'graphical' in some parts of the documentation.)

Analyses of Secondary Efficacy Objectives

The analyses of insulin dose (i.e., actual and change from baseline in total, basal, prandial insulin dose and prandial/total insulin dose ratio) used an MMRM model similar to that for the primary outcome with an additional term of HbA1c stratum (≤8.0%, >8.0%).

Treatment comparisons for the proportion of patients with HbA1c <7.0% and <7.5% were analysed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model, including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c-by-visit interaction, and treatment-by-visit interaction. An unstructured covariance structure was used. As a sensitivity analysis, the proportion of patients with HbA1c <7.0% and <7.5% at Week 26 (Visit 15), imputed using LOCF, was compared using a logistic regression model with terms for treatment and baseline HbA1c value.

There was a substudy on health-related quality of life (HRQoL), conducted in English-speaking countries. The protocol and statistical analysis plan (SAP) for this substudy were missing from the submission and were requested to be submitted. The MAH submitted upon request the protocol which included the SAP. Patients and caregivers who were enrolled at sites in the US and who spoke English were asked to participate in Pediatric Quality-of-Life addendum I8B-MC-ITSB(1) using the measure PedsQL, consisting of PedsQL Generic Core Multidimensional Scales (physical functioning, emotional functioning, social functioning, school functioning), Summary Scores (psychosocial health summary score, physical health

summary score, total score), and Diabetes Module (diabetes, treatment I, treatment II, worry, communication). For the PedsQL Generic Core (4.0) and PedsQL Diabetes (3.2) scales, transformation of scores was needed as indicated by the scoring manual. Items were scored on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Items were then reversed scored as follows: 0=100, 1=75, 2=50, 3=25, 4=0. The dimension scores and the summary scores were calculated by summing the transformed scores of the items divided by the number of items answered. Moreover, for both the PedsQL Generic Core (4.0) and PedsQL Diabetes (3.2) scales, if more than 50% of the items in the scale were missing, then the Scale Scores were not computed. If 50% or more items were completed, mean of the completed items in a scale was used to impute the missing scores.

The PedsQL Diabetes (3.2) and PedsQL Generic Core (4.0) scales were analysed by ANCOVA model using treatment and strata (pooled country, type of basal insulin, and HbA1c stratum) as fixed effects and baseline score as a covariate. The analyses covered the total scores, all subscale scores, and dimensions.

Analyses of Exploratory Objectives

Seven-point SMBG assessment covered three, approximately 2-week intervals prior to baseline, week 12 and week 24. For each of the three interval (referred to as 'visits' hereafter), 7-point SMBG was to be conducted on at least 3 nonconsecutive days. The following variables were derived from the 7-point SMBG profiles for each visit and analysed using the MMRM model similar to that for the primary outcome with an additional term of HbA1c stratum (≤8.0%, >8.0%):

- 1-hour postmeal excursion
- between-day coefficient of variation (CV) and SD, and
- within-day CV and SD.

The excursion of SMBG was calculated for each meal category (morning meal, midday meal, evening meal, and all meals). The average value of excursions from the same visit for each patient was used in the analysis.

Blood glucose (BG) values that were out of the detectable range (BG <20 mg/dL [1.1 mmol/L] or BG >600 mg/dL [33.3 mmol/L]) of the glucometer were excluded from the analysis data. For baseline SMBG, records that were collected on or after the first dose date were excluded from the analysis. If there were multiple records on the same day and same time point, only the last entry was used for variable derivation. Blood glucose readings without units were not used in the analysis.

At a given visit, the CV and SD on each day with the 7-point SMBG profile were calculated using all the glucose values within that day. The average values of these CVs and SDs were then used as the within-day CV and SD at that visit in analysis. At a given visit, the CV and SD at each of the 7 pre-specified SMBG time points were calculated using the corresponding glucose values of the 7-point SMBG profiles. The average values of these CVs and SDs was then used as the between-day CV and SD at that visit in analysis.

2.4.1.2. Results

2.4.1.2.1. Participant flow

The patient disposition from enrolment to randomisation is given in Figure 18 and from randomisation to safety follow-up in Figure 19.

Figure 18 Study participant disposition prerandomisation

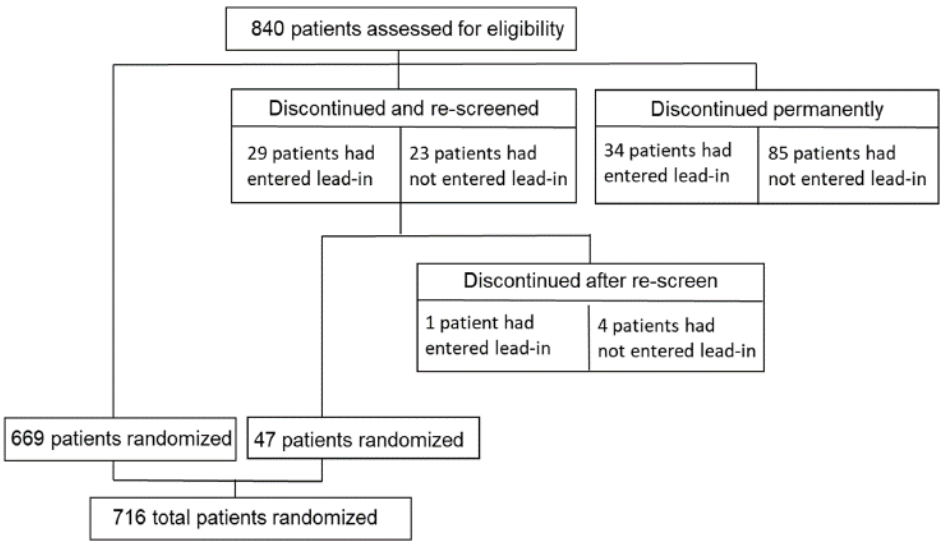
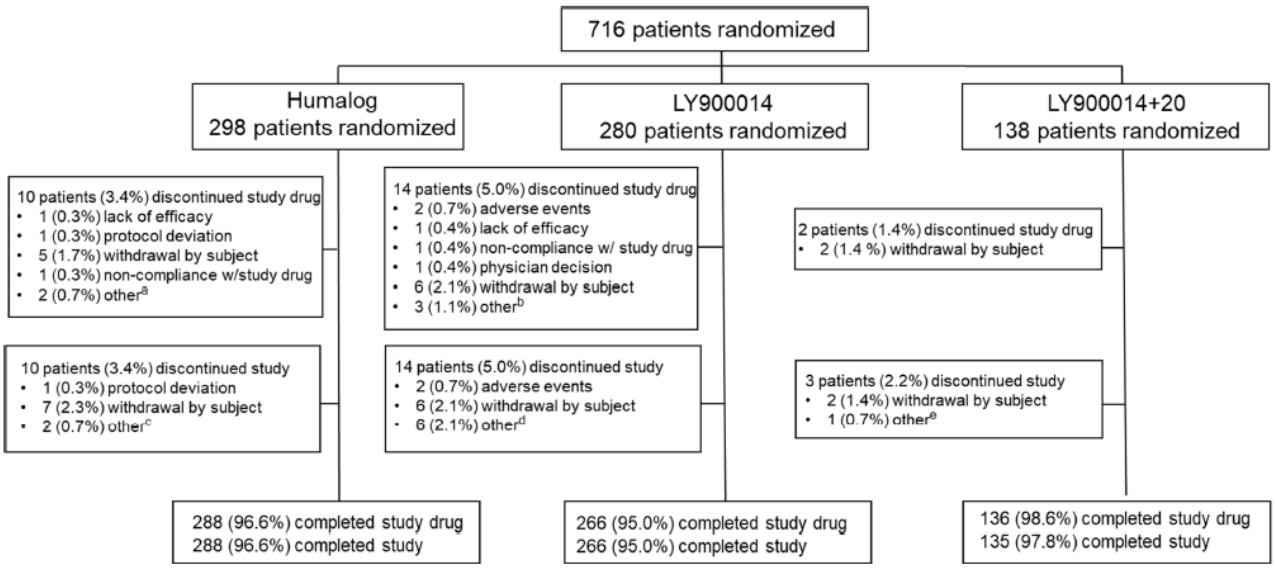


Figure 19 Study participant disposition post-randomisation



Abbreviation: COVID-19 = coronavirus disease 2019.

a Reasons for discontinuation: too much stress (1 patient) and COVID-19 pandemic (1 patient).

b Reasons for discontinuation: increased burden of study procedures (1 patient), COVID-19 pandemic (1 patient), and terminated by sponsor (1 patient).

c Reasons for discontinuation: terminated by sponsor (1 patient) and insulin pump (1 patient).

d Reasons for discontinuation: moving due to COVID-19 pandemic (1 patient), stress due to COVID-19 pandemic (1 patient), COVID -9 pandemic (1 patient), early discontinuation by Lilly medical advisor due to failure of inclusion criteria (1 patient), patient not completing diary (1 patient), and insulin painful to patient (1 patient).

e Reasons for discontinuation: moved due to COVID-19 pandemic (1 patient).

Approximately 96% of patients across treatment groups completed the study while on study drug. The most common reason for discontinuation of study and/or study drug was withdrawal by subject.

2.4.1.2.2. Recruitment

Study ITSB was conducted at 96 centres that enrolled participants in the United States, Russian Federation, Czech Republic, Spain, Ukraine, Brazil, Israel, France, Italy, Poland, United Kingdom, Mexico, China, Austria, Germany, Denmark, and Japan. First patient visit: 07 April 2019, last patient visit: 02 July 2021.

2.4.1.2.3. Conduct of the study

The MAH confirms that the study was conducted in accordance with the protocol, consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH GCP Guidelines, and applicable laws and regulations.

Amendments

The protocol and protocol amendments located in an appendix of the CSR provide information about changes in study conduct implemented by protocol amendments. The changes made in protocol amendments were considered nonsubstantial. All amendments are not described in this AR for brevity. ITSB Amendment (a) included, e.g., addition of CGM/FGM and relevant advice for their use, more flexibility to glucose monitoring and requirement to confirm any suspected hypoglycaemia events by BG meter. ITSB Amendment (b) included, e.g., changes in daily insulin dose range to allow for younger and active children using smaller doses and adolescents who require more insulin during puberty; allowed rescreen to patients who had a screen fail or unexpectedly had to discontinue due to COVID-19 enrolment pause.

Table 24 summarizes the approval dates of the protocol and subsequent amendments in addition to providing the date of the first patient visit.

Table 24 Protocol Approval Dates and First Patient Visit Date

Milestone	Date
ITSB approval	26 October 2018
First patient visit	07 April 2019
ITSB (a) approval	18 November 2019
ITSB (b) approval	30 April 2020

Protocol deviations

Important protocol deviations are defined as those likely to have a significant impact on the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

A total of 78 participants (10.9%) had at least 1 important protocol deviation. The most common important protocol deviations were related to IP treatment assignment/randomisation error (n=24 [3.4%]), informed consent (n=22 [3.1%]), and study procedures (n=22 [3.1%]).

There were 8 patients (1.1%) with protocol deviations due to inadvertent enrolment. Seven of these patients were considered inadvertent enrolment due to misinterpretation of Inclusion Criterion [9], Female patients of childbearing potential. Due to the misinterpretation of the protocol definition of childbearing potential, some female participants had missing pregnancy tests at Visits 1 and 4. All protocol deviations related to IP treatment assignment/randomisation error were due to IWRS entry error impacting stratification. Several subjects had office visits changed to telephone visits due to COVID-19 restrictions, leading to missing patient characteristics or laboratory values for the visit.

Important protocol deviations are listed in Appendix 18 of the CSR and not listed here for brevity.

2.4.1.2.4. Baseline data

The study groups were comparable for demographic and baseline characteristics (Table 25)

Table 25 Summary of Demographic and Diabetes Characteristics

Parameter	Humalog (N=298)	LY900014 (N=280)	LY900014+20 (N=138)	Total (N=716)	p-Value[a]
Sex, n (%)					
Female	140 (47.0)	144 (51.4)	65 (47.1)	349 (48.7)	0.515
Male	158 (53.0)	136 (48.6)	73 (52.9)	367 (51.3)	
Age (years)					
Mean (SD)	12.39 (3.18)	12.10 (3.42)	12.32 (3.75)	12.26 (3.39)	0.593
Minimum, Maximum	3, 17	3, 17	4, 17	3, 17	
Age Group 1, n (%)					
1 to <12 years	105 (35.2)	98 (35.0)	50 (36.2)	253 (35.3)	0.969
12 to <18 years	193 (64.8)	182 (65.0)	88 (63.8)	463 (64.7)	
Age Group 2, n (%)					
1 to <6 years	7 (2.3)	10 (3.6)	10 (7.2)	27 (3.8)	0.163
6 to <12 years	98 (32.9)	88 (31.4)	40 (29.0)	226 (31.6)	
12 to <18 years	193 (64.8)	182 (65.0)	88 (63.8)	463 (64.7)	
Race, n (%)					
American Indian or Alaska Native	6 (2.0)	6 (2.1)	0	12 (1.7)	0.227
Asian	20 (6.7)	13 (4.6)	7 (5.1)	40 (5.6)	
Black or African American	7 (2.3)	3 (1.1)	1 (0.7)	11 (1.5)	
Multiple	4 (1.3)	0	1 (0.7)	5 (0.7)	
Native Hawaiian or Other Pacific Islander	2 (0.7)	0	0	2 (0.3)	
Not Reported	3 (1.0)	2 (0.7)	3 (2.2)	8 (1.1)	
White	256 (85.9)	256 (91.4)	126 (91.3)	638 (89.1)	
Ethnicity, n (%)					
Hispanic or Latino	12 (24.0)	12 (22.6)	6 (25.0)	30 (23.6)	0.972
Not Hispanic or Latino	38 (76.0)	41 (77.4)	18 (75.0)	97 (76.4)	
BMI (kg/m^2)					
Mean (SD)	20.3 (4.19)	20.5 (4.60)	20.5 (4.39)	20.4 (4.39)	0.805
Minimum, Maximum	12.8, 38.8	11.5, 38.0	14.1, 37.3	11.5, 38.8	
Duration of Diabetes (years)					
Mean (SD)	4.7 (3.28)	4.5 (3.58)	4.6 (3.32)	4.6 (3.41)	0.738
Minimum, Maximum	0.5, 15.9	0.5, 16.5	0.5, 15.3	0.5, 16.5	
HbA1c, Mean (SD)					
Screening (%)	7.87 (0.88)	7.91 (0.89)	7.84 (0.85)	7.88 (0.87)	0.721
Screening (mmol/mol)	62.51 (9.57)	62.93 (9.68)	62.15 (9.28)	62.60 (9.55)	

Table 26 Summary of Demographic and Diabetes Characteristics (continued)

Parameter	Humalog (N=298)	LY900014 (N=280)	LY900014+20 (N=138)	Total (N=716)	p-Value[a]
Baseline (%)	7.81 (0.91)	7.81 (0.87)	7.77 (0.85)	7.80 (0.88)	0.860
Baseline (mmol/mol)	61.85 (9.99)	61.91 (9.50)	61.38 (9.31)	61.78 (9.66)	
HbA1c, Baseline Stratum, n (%)					
≤8.0%	187 (62.8)	174 (62.1)	86 (62.3)	447 (62.4)	0.988
>8.0%	111 (37.2)	106 (37.9)	52 (37.7)	269 (37.6)	
Prestudy Bolus Insulin, n (%)					
Insulin aspart	134 (45.0)	128 (45.7)	62 (44.9)	324 (45.3)	0.877
Insulin fiasp	4 (1.3)	2 (0.7)	0	6 (0.8)	
Insulin glulisine	28 (9.4)	29 (10.4)	13 (9.4)	70 (9.8)	
Insulin lispro	132 (44.3)	121 (43.2)	63 (45.7)	316 (44.1)	
Bolus Insulin Dosing Plan, n (%)					
Carbohydrate Counting	234 (78.5)	219 (78.2)	116 (84.1)	569 (79.5)	0.330
Pattern Adjustment	64 (21.5)	61 (21.8)	22 (15.9)	147 (20.5)	
Lead-in Basal Insulin, n (%)					
Insulin degludec	108 (36.2)	105 (37.5)	46 (33.3)	259 (36.2)	0.791
Insulin detemir	26 (8.7)	23 (8.2)	16 (11.6)	65 (9.1)	
Insulin glargine	164 (55.0)	152 (54.3)	76 (55.1)	392 (54.7)	
Personal CGM Use, n (%)					
Yes	128 (43.0)	119 (42.5)	61 (44.2)	308 (43.0)	0.946

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

[a] p-Value for overall treatment effect.

Output Location: /lillyce/prd/ly900014/i8b_mc_itsb/final/output/shared/ards/Table_11_1.rtf.

Only 27 patients were below the age of 6, of whom 10 in the LY900014 group and 10 in the LY900014 group (Table 27). No subjects below the age of 3 years were included in the study.

2.4.1.2.5. Exposure

Exposure to investigation product over the study is shown in table 27. The exposure from first to last dose on IP in total patient-years was 136.3 for LY900014, 146.9 for Humalog, and 68.8 for LY900014+20.

Table 27 Summary of Exposure to IP From Randomization to Week 26 All Randomized Patients

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

2.4.1.2.6. Outcomes and estimation

Primary and Multiplicity-Controlled Efficacy Analyses

Primary objective: change in HbA1c with LY900014 vs. Humalog, noninferiority

The primary objective was achieved. LY900014 was noninferior to Humalog for glycaemic control. The upper limit of the 95% CI for the difference in change in HbA1c was less than the prespecified NIMs of 0.4% and 0.3% for both the efficacy and the ITT estimands (table 28)

Table 28 Summary and Analysis of HbA1c at Baseline and Week 26

Treatment Group	HbA1c, LSM (SE)			LSM Difference at Week 26 A: LY900014 versus Humalog (95% CI), p-value B: LY900014 + 20 versus Humalog (95% CI), p-value C: LY900014 + 20 versus LY900014 (95% CI), p-value
	Baseline	Week 26	Change from Baseline at Week 26	
Efficacy Estimand, HbA1c (%)[a]				
Humalog	7.81 (0.05)	7.88 (0.05)	0.09 (0.05)	A: -0.02 (-0.17, 0.13), p=0.783
LY900014	7.78 (0.05)	7.85 (0.05)	0.06 (0.05)	B: -0.02 (-0.20, 0.17), p=0.867
LY900014 + 20	7.77 (0.07)	7.86 (0.08)	0.07 (0.08)	C: 0.01 (-0.18, 0.19), p=0.956
ITT Estimand, HbA1c (%)[b,c,d]				
Humalog	7.81 (0.05)	7.87 (0.05)	0.06 (0.05)	A: -0.01 (-0.15, 0.14), p=0.915
LY900014	7.81 (0.05)	7.86 (0.05)	0.06 (0.05)	B: -0.00 (-0.18, 0.18), p=0.966
LY900014 + 20	7.77 (0.08)	7.86 (0.08)	0.06 (0.08)	C: 0.00 (-0.18, 0.19), p=0.965
Efficacy Estimand, HbA1c (mmol/mol)[a]				
Humalog	61.84 (0.56)	62.57 (0.57)	0.94 (0.57)	A: -0.23 (-1.84, 1.39), p=0.783
LY900014	61.57 (0.58)	62.35 (0.59)	0.71 (0.59)	B: -0.17 (-2.15, 1.81), p=0.867
LY900014 + 20	61.38 (0.82)	62.41 (0.83)	0.77 (0.83)	C: 0.06 (-1.95, 2.06), p=0.956
ITT Estimand, HbA1c (mmol/mol)[b,c,d]				
Humalog	61.85 (0.56)	62.49 (0.56)	0.71 (0.56)	A: -0.09 (-1.69, 1.51), p=0.915
LY900014	61.91 (0.58)	62.41 (0.59)	0.62 (0.59)	B: -0.04 (-2.00, 1.91), p=0.966
LY900014 + 20	61.38 (0.82)	62.45 (0.82)	0.67 (0.82)	C: 0.04 (-1.94, 2.03), p=0.965

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; HbA1c = hemoglobin A1c; LSM = least-squares mean; LY900014 + 20 = LY900014 dose given up to 20 minutes after the start of the meal; MMRM = mixed-effects model of repeated measures; N = number of randomized subjects; SE = standard error; ITT = intention-to-treat.

[a] MMRM model for postbaseline measures: Variable = baseline + pooled country + type of basal insulin at randomization + age group 1 + treatment + time + treatment*time (Type III sum of squares).

[b] Baseline multiple imputation model for endpoint measures: Variable = baseline + pooled country + type of basal at randomization + age group 1 + treatment (Type III sum of squares).

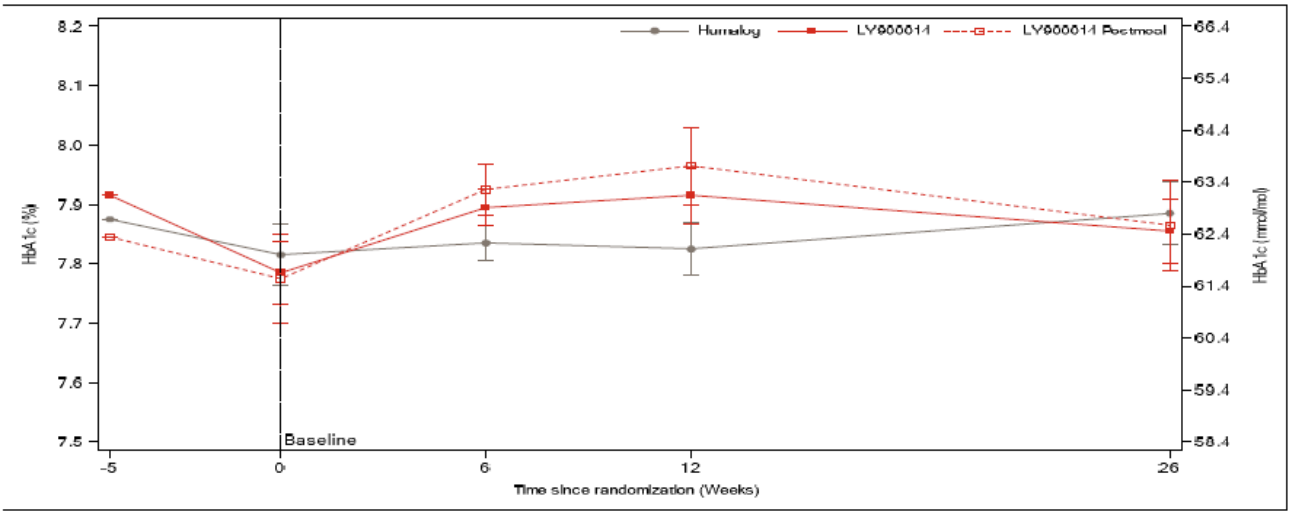
[c] At Week 26, HbA1c was missing for 16 subjects (5.4%), 20 subjects (7.1%), and 7 subjects (5.1%) for Humalog, LY900014, and LY900014 + 20, respectively.

[d] The missing data at Week 26 were imputed by return to baseline approach (1000 imputed datasets with random number seed 123456). After imputation, LSM and p-values were calculated from ANCOVA, adjusted for baseline and other stratification factors.

Note: Number of randomized subjects: Humalog, N = 298; LY900014, N = 280; LY900014 + 20, N = 138.

There were no significant differences in HbA1c between treatment groups at any visit. For both LY900014 and LY900014+20 treatment groups, there were significant within-treatment changes at Weeks 6 and 12 but not at Week 26. Figure 20 presents the actual LS mean HbA1c by visit and at endpoint from all randomized patients from study entry to Week 26 for the efficacy estimand.

Figure 20 Plot of HbA1c (%, mmol/mol) by visit



Abbreviations: HbA1c = hemoglobin A1c; LSM = least-squares mean; LY900014 Postmeal = LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal; SEM = standard error of mean.

Note 1: The conversion between % and mmol/mol is 10.93*HbA1c(%) - 23.5
Note 2: Data are mean at study entry and LSM ± SEM at other visits.

Table 29 presents a summary of the results of analyses using the graphical approach for the primary and multiplicity-controlled objectives.

Table 29 Summary of Results from the Primary and Multiplicity-Controlled Efficacy Analyses Using the Graphical Approach

		Test	LSM (SE)		LSM Diff (95% CI)	p-Value	NIM	Objective Met?
Primary Objective			**Humalog**	**LY900014**				
Efficacy Estimand	Change in HbA1c (%)	NI	0.09 (0.05)	0.06 (0.05)	-0.02 (-0.17, 0.13)		0.4	Yes
	Change in HbA1c (mmol/mol)	NI	0.94 (0.57)	0.71 (0.59)	-0.23 (-1.84, 1.39)		4.4	Yes
ITT Estimand[a]	Change in HbA1c (%)	NI	0.06 (0.05)	0.06 (0.05)	-0.01 (-0.15, 0.14)		0.4	Yes
	Change in HbA1c (mmol/mol)	NI	0.71 (0.56)	0.62 (0.59)	-0.09 (-1.69, 1.51)		4.4	Yes
Multiplicity-Controlled	**Objective 1**		**Humalog**	**LY900014+20**				
Efficacy Estimand	Change in HbA1c (%)	NI	0.09 (0.05)	0.07 (0.08)	-0.02 (-0.20, 0.17)		0.4	Yes
	Change in HbA1c (mmol/mol)	NI	0.94 (0.57)	0.77 (0.83)	-0.17 (-2.15, 1.81)		4.4	Yes
ITT Estimand[a,b]	Change in HbA1c (%)	NI	0.06 (0.05)	0.06 (0.08)	-0.00 (-0.18, 0.18)		0.4	Yes
	Change in HbA1c (mmol/mol)	NI	0.71 (0.56)	0.67 (0.82)	-0.04 (-2.00, 1.91)		4.4	Yes
Multiplicity-Controlled	**Objective 2**		**Humalog**	**LY900014**				
Efficacy Estimand	Change in HbA1c (%)	SUP	0.09 (0.05)	0.06 (0.05)	-0.02 (-0.17, 0.13)	0.783		No
	Change in HbA1c (mmol/mol)	SUP	0.94 (0.57)	0.71 (0.59)	-0.23 (-1.84, 1.39)	0.783		No
ITT Estimand[a,b]	Change in HbA1c (%)	SUP	0.06 (0.05)	0.06 (0.05)	-0.01 (-0.15, 0.14)	0.915		No
	Change in HbA1c (mmol/mol)	SUP	0.71 (0.56)	0.62 (0.59)	-0.09 (-1.69, 1.51)	0.915		No

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; Diff = difference; HbA1c = hemoglobin A1c; ITT = intention-to-treat; LSM = least-squares means; N=number of subjects; NI = noninferiority comparison; NIM = noninferiority margin; SE = standard error; SUP = superiority comparison.

Note: Number of randomized subjects: Humalog, N=298; LY900014, N=280; and LY900014+20, N=138.

[a] At Week 26, HbA1c was missing for 16 subjects (5.4%), 20 subjects (7.1%) and 7 subjects (5.1%) for Humalog, LY900014 and LY900014+20, respectively.

[b] The missing data at Week 26 were imputed by return to baseline approach (1000 imputed datasets with random number seed 123456). After imputation, least-squares means and p-values were calculated from ANCOVA, adjusted for baseline and other stratification factors.

Multiplicity-Controlled Objective (1): change in HbA1c with LY900014 + 20 vs. Humalog

Multiplicity-Controlled Objective (1) was achieved. LY900014 + 20 was noninferior to Humalog for glycaemic control. The upper limit of the 95% CI for the difference in change in HbA1c was less than the prespecified NIM of 0.4% and 0.3% for both the efficacy and the ITT estimands. (Table 30).

Multiplicity-Controlled Objective (2): change in HbA1c with LY900014 vs. Humalog, superiority

The Multiplicity-Controlled Objective (2) was not achieved. LY900014 was not statistically superior to Humalog for glycaemic control with the efficacy or the ITT estimand (Table 31).

Secondary and Tertiary Efficacy Analyses

Analyses of the secondary and tertiary endpoints were not multiplicity controlled.

Proportion of patients achieving HbA1c targets

There were no statistically significant treatment differences among the LY900014, LY900014+20, or Humalog treatment groups in the percentages of patients achieving HbA1c targets (<7%, 53 mmol/mol, and <7.5%, 58 mmol/mol) at Week 26. At week 26, around 20% of subjects reached HbA1c <7.0% (53 mmol/mol) (table 32). For the threshold of HbA1c 7.5%, the respective proportions were 40.1%, 37.0% and 33.3 % for Humalog, LY900014, and LY900014+20, respectively.

Table 30 Proportion of Patients Achieving HbA1c Target <7.0% (53 mmol/mol) From Randomization to Week 26 Prior to Discontinuation of IP, All Randomized Patients

Variable Analyzed: HbA1c <7.0%

				Odds Ratio (95% CI)			Pairwise p-value		
Time Point	Humalog (N = 298)	LY900014 (N = 280)	LY900014 Postmeal (N = 138)	LY900014 Postmeal vs Humalog	LY900014 Postmeal vs LY900014	LY900014 vs Humalog	LY900014 Postmeal vs Humalog	LY900014 Postmeal vs LY900014	LY900014 vs Humalog
Baseline	54(18.37)	47(17.22)	22(15.94)	0.85 (0.50, 1.46)	0.92 (0.53, 1.60)	0.93 (0.60, 1.42)	0.562	0.769	0.724
Week 6 (Visit 7)	47(16.38)	37(13.96)	26(19.40)	1.50 (0.70, 3.25)	1.88 (0.84, 4.23)	0.80 (0.41, 1.55)	0.299	0.125	0.506
Week 12 (Visit 10)	58(20.79)	38(14.62)	23(17.04)	0.65 (0.35, 1.22)	1.18 (0.60, 2.29)	0.55 (0.32, 0.97)	0.177	0.634	0.037
Week 26 (Visit 15)	56(20.00)	57(21.92)	25(19.08)	0.93 (0.49, 1.75)	0.75 (0.39, 1.43)	1.23 (0.76, 2.00)	0.814	0.384	0.396
LOCF Endpoint	58(19.73)	59(21.61)	26(18.84)	0.92 (0.50, 1.69)	0.76 (0.42, 1.39)	1.21 (0.75, 1.95)	0.796	0.377	0.428

Abbreviations: CI = confidence interval; IP =investigational product; LY900014 Postmeal = LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal; N = number of subjects in the population with baseline and post-baseline value at the specified time point; n = number of subjects in the specified category; NC = not calculable.

Note: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
*a - Odds ratio, CI, and p-value for baseline measures are from logistic regression model with Treatment as factor.
*b - Odds ratio, CI, and p-value for LOCF endpoint measures are from logistic regression model with Treatment and baseline as covariates
*c - Odds ratio, CI, and p-value for post-baseline measures are from longitudinal logistic regression model with Treatment, Time, Baseline HbA1c, Baseline HbA1c-by Time, and Treatment by Time interaction as covariates, and Variance-Covariance structure = unstructured

Insulin dose

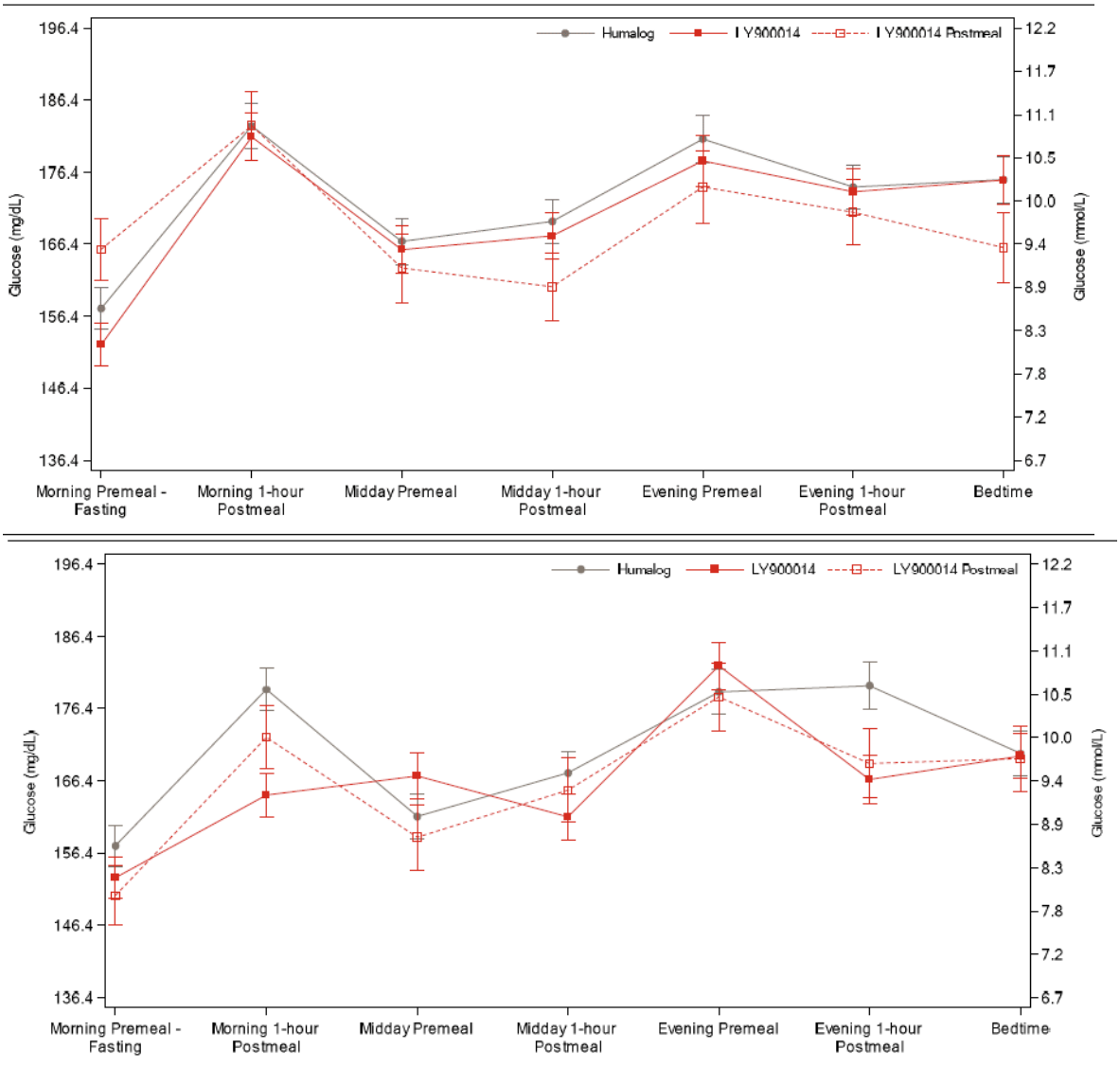
There were no statistically significant treatment differences at baseline and Week 26 for total insulin, basal insulin, prandial insulin, or prandial/total insulin dose ratios. (data not shown for brevity)

7-point SMBG results

Postprandial glucose

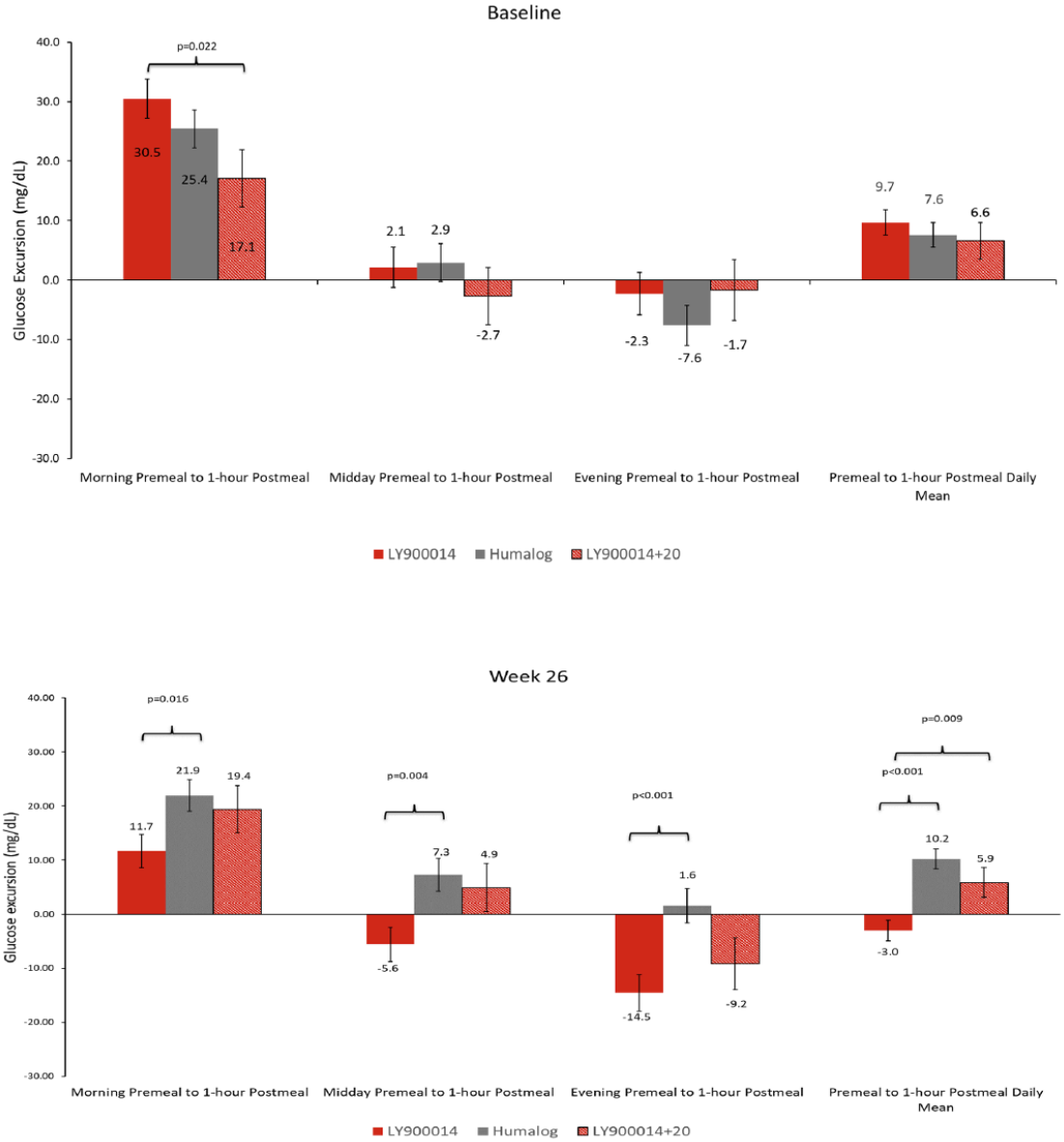
At Week 26, premeal to 1-hour postmeal excursions were lower with LY900014 than with Humalog at Week 26 at morning and evening meals (Figures 5.4.2.2.6.2 and 5.4.2.2.6.3).

Figure 20 Time course of 7-point self-monitored blood glucose profile (mg/dL and mmol/L) at baseline (top panel) and Week 26 (bottom panel).



Abbreviations: BG = blood glucose; LSM = least-squares mean; LY900014 Postmeal = LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal; SEM = standard error of mean.
Note 1: 1 mg/dL = 0.0555 mmol/L.
Note 2: Data are LSM ± SEM.
Note 3: LY900014 had statistically significantly lower BG values at the morning (p<.001) and evening (p=0.006) 1-hour postmeal time points and for the 1-hour postmeal daily mean (p=0.001)

Figure 21 Postprandial glucose excursions from SMBG at baseline (top panel) and Week 26 (bottom panel)



Abbreviation: LY900014 + 20 = LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal.

Data are LSmean ± SEM.
ANOVA model for baseline Premeal to 1-hour Postmeal Excursion = Treatment (Type III sum of squares).
MMRM for Premeal to 1-hour Postmeal Excursion = Baseline + Pooled Country + HbA1c Stratum + Type of Basal Insulin at Randomization + Pooled Age Group 1 + Treatment + Time + Treatment*Time. Unstructured variance-covariance matrix.

Change from baseline (CFB) in mean PPG excursions from premeal to 1 h postmeal at week 26 for each meal are presented in table 31. The CFB in daily mean reduction in PPG excursion (1 hour) for premeal and postmeal administrated LY900014 is also given in Table 32.

The daily mean 1-h PPG excursions for LY900014 vs. Humalog were

- actual value: −0.2 mmol/L (−3.0 mg/dL) versus 0.6 mmol/L (10.2 mg/dL), and
- change from baseline: −0.6 mmol/L (−11.3 mg/dL) versus 0.1 mmol/L (1.9 mg/dL).

Table 31 Premeal to 1-hour Postmeal Excursions (change from baseline), Humalog vs. LY900014 at Week 26

Effect	Short Description	Comparator	Treatment	
PPG Excursions		Mealtime[a] Humalog	Mealtime[a] LY900014	LSM Diff (95% CI)
Morning premeal to 1 hr postmeal PPG excursion reduction	LS Mean (SE) CFB at 26 wks (mg/dL)	-4.3 (2.93)	-14.5 (3.07)	-10.2 (-18.6, -1.9)
	LS Mean (SE) CFB at 26 wks (mmol/L)	-0.2 (0.16)	-0.8 (0.17)	-0.6 (-1.0, -0.1)
Midday premeal to 1 hr postmeal PPG excursion reduction	LS Mean (SE) CFB at 26 wks (mg/dL)	5.4 (3.03)	-7.4 (3.19)	-12.8 (-21.5, -4.2)
	LS Mean (SE) CFB at 26 wks (mmol/L)	0.3 (0.17)	-0.4 (0.18)	-0.7 (-1.2, -0.2)
Evening premeal to 1 hr postmeal PPG excursion reduction	LS Mean (SE) CFB at 26 wks (mg/dL)	5.7 (3.20)	-10.4 (3.38)	-16.1 (-25.3, -6.9)
	LS Mean (SE) CFB at 26 wks (mmol/L)	0.3 (0.18)	-0.6 (0.19)	-0.9 (-1.4, -0.4)
PPG Excursions		Mealtime[a] LY900014	LY900014 +20[a]	LSM Diff (95% CI)
Premeal to 1 hr postmeal excursion daily mean reduction	LS Mean (SE) CFB at 26 wks (mg/dL)	-11.3 (1.94)	-2.5 (2.76)	8.9 (2.2, 15.5)
	LS Mean (SE) CFB at 26 wks (mmol/L)	-0.6 (0.11)	-0.1 (0.15)	0.5 (0.1, 0.9)

Note: The data are based on a MMRM: Premeal to 1-hour Postmeal Excursion = Baseline + Pooled Country + HbA1c Stratum + Type of Basal Insulin at Randomization + Pooled Age Group 1 + Treatment + Time + Treatment*Time (Type III sum of squares). Unstructured variance-covariance matrix.

Glycaemic variability

Within-day and between-day glycaemic variability was measured by the standard deviation and the coefficient of variation of 7-point SMBG profiles. No significant differences were observed in within-day or between-day glycaemic variability between treatment groups at baseline and at Week 26 (data not shown for brevity).

Body weight

Weight increased similarly in all study arms, with median change from baseline of 2.1, 1.9 and 2.0 kg in the Humalog, LY900014 and LY900014 + 20 groups, respectively. Median growth in height was 2.0 cm in all three study arms.

Health outcomes analyses

In the Pediatric Quality-of-Life addendum I8B-MC-ITSB(1) using the measure PedsQL (description in Section 2.4.1.1.10), some differences were seen at baseline between study arms. However, at the LOCF endpoint, no differences were seen between treatments (data not shown for brevity).

2.4.1.2.7. Ancillary analyses

Primary outcome

Additional analyses of HbA1c were conducted for the efficacy estimand for the Completer Population and the Per Protocol Population, respectively. Results were consistent with those from the All Randomized Population, and all noninferiority objectives were met. (data not shown for brevity)

The progressive stress test sensitivity analysis of HbA1c (%) for the efficacy estimand and ITT estimand implied that the primary results are robust and support conclusions made for the primary objective (data not shown for brevity).

Subgroup analyses

Subgroup analyses for actual HbA1c and HbA1c change from baseline were performed to examine whether the treatment difference varied by the subgroup. The evaluation was based on the treatment-by-subgroup interaction using either the efficacy or ITT estimand with multiple imputation described for the primary analysis with the addition of subgroup-related terms. The treatment-by-subgroup interaction effect at Week 26 was evaluated at the significance level of 0.10.

There were no significant treatment-by-subgroup interactions for age groups, BMI, HbA1c stratum, duration of diabetes, ethnicity, country, type of basal insulin, prandial insulin dosing plan, personal CGM/FGM use, and treatment-emergent anti-drug antibodies (TEADA) status for the efficacy estimand or ITT estimand. In different age groups, the mean HbA1c (% / mmol/mol) in the Humalog, LY900014 and LY900014+20 groups, respectively, was at Week 26

- 8.02 / 64.2, 7.89/ 62.7 and 7.59 / 59.5 in subjects aged 3 to <6 years;
- 7.72 / 60.9, 7.85 / 62.3, and 7.99 / 63.8 in subjects aged 6 to <12 years, and
- 7.98 / 63.4, 7.86 / 62.2 and 7.78/ 61.8 in subjects aged 12 to <18 years.

Statistically significant treatment-by-subgroup interactions were observed for gender and race for the ITT estimand and for region for the efficacy estimand. These subgroup interactions were not considered clinically meaningful (data not shown for brevity).

2.4.1.3. ITSB CGM Addendum

2.4.1.3.1. Methods

Study I8B-MC-ITSB (ITSB) CGM addendum was performed in a subset of sites that participated in the main study. The original submission included only the CSR for the CGM Addendum, but the appendices of this substudy – protocol, statistical analysis plan (SAP), ERB list and sample ICF – were not included. These documents were requested and received with the response from the MAH, except for the SAP. The

methodology for the derivation of the primary endpoint, $iAUC_{0\text{-}2\ hours}$ for each visit, and some other variables derived from CGM data, is not included in the protocol or the CSR**.** Since the CGM Addendum failed to recruit an adequate number of subjects and therefore did not have the power to show differences between treatments, the results of the CGM are not considered crucial for the assessment and the issue of the missing SAP is not pursued further.

Design of Addendum

These sites were selected in countries where Dexcom G6 is approved for use in children. This resulted in 20 centres that screened participants in Israel, Italy, Poland, Spain, and the US. Due to the limited number of countries where Dexcom G6 was approved for use in children and the non-obligatory nature of the CGM addendum, the CGM addendum did not meet the prespecified enrolment criteria.

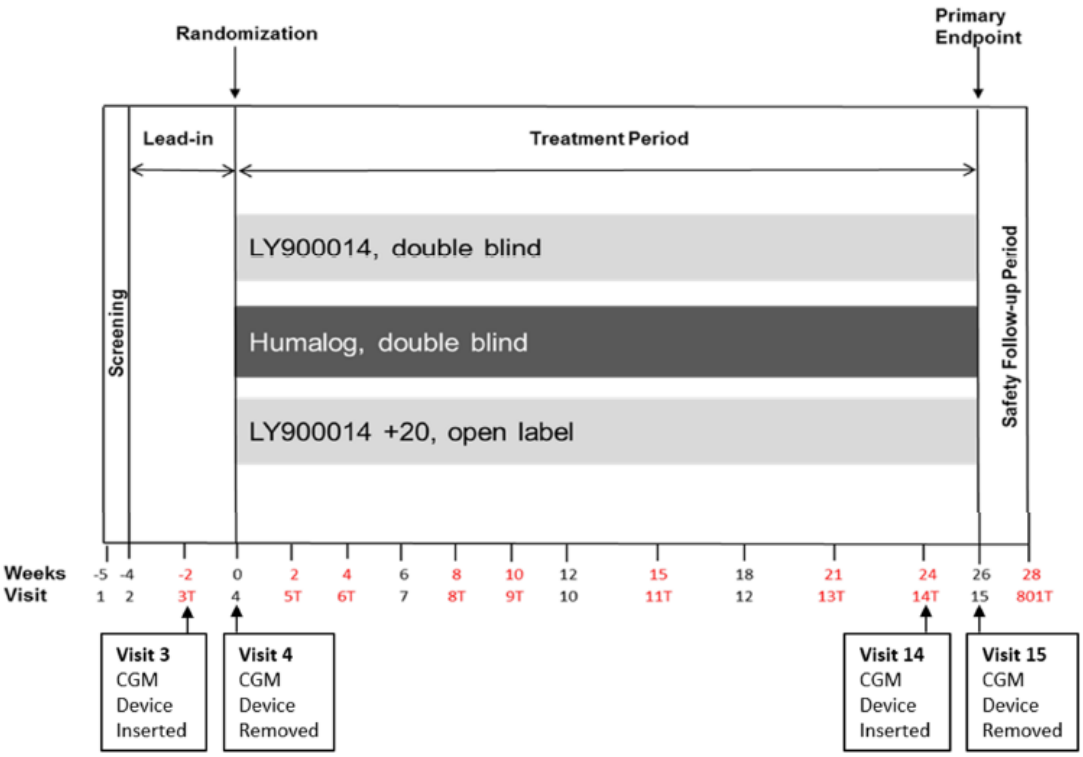
The purpose of this addendum was to evaluate the 24-hour glucose profile captured with continuous glucose monitoring (CGM) for LY900014 and Humalog, when either is used in combination with basal insulin as part of a multiple daily injection regimen.

In addition to use of the CGM device, the same intervention measures from the main Study ITSB applied to all patients enrolled in the CGM addendum.

Eligible subjects were required to be participants in Study ITSB for participation in this Addendum. Patients or parents (or legal representative) signed separate addendum-specific informed consents. Age was limited to the approved Dexcom G6 indication for use in the geographic region where it was used.

The study included a 1-week screening with a 4-week lead-in period, followed by a 26-week treatment period and a 2-week safety follow-up period. In 2 of the treatment groups, LY900014 and Humalog were administered immediately (0 to 2 minutes) prior to each meal in a double-blind manner. A third open-label treatment group consisted of LY900014 administered up to 20 minutes after the start of a meal (LY900014+20). (Figure 22)

Figure 22 ITSB CGM addendum study design.



Abbreviations: CGM = continuous glucose monitoring; COVID-19 = coronavirus disease 2019.
Note: Study visits in red text =telephone visits. LY900014+20 = open-label LY dose given up to 20 minutes after the start of the meal. Double-blind groups = Dose given 0-2 minutes prior to the start of the meal. Visits 3 and 14 were supposed to change to office visits for CGM sensor insertion; however, due to the COVID-19 pandemic, Visit 14 was kept as a telephone visit for those patients who were capable of inserting the CGM by themselves.

Patients who chose to participate in the Study ITSB CGM addendum used the CGM device during 2 periods of time: during the 4-week lead in period, and during the 26-week treatment period.

Sample size

Approximately 163 randomized patients were planned to participate in this addendum so that 130 patients would complete this addendum at Week 26. Assuming a mean difference of 22 mg·h/dL, an SD of 39.5 mg·h/dL, and a 2-sided significance level of 0.05, approximately 52 completers in each double-blind treatment group would provide approximately 80% power to show superiority of LY900014 versus Humalog in the iAUC0-2 hours after the start of meals obtained from up to 10 days of CGM use at Week 26. Assuming a 20% dropout rate for 26 weeks, approximately 163 patients (65 in each double-blind treatment group and 33 in the open-label treatment group) were planned to participate in this addendum.

Objectives

The primary outcome of the CGM addendum was the $iAUC_{0\text{-}2\ hours}$ after meals obtained from up to 10 days of CGM use prior to Week 26.

An analysis of covariance model with treatment, type of basal insulin, HbA1c stratum (≤8.0% or >8.0%), and age group as fixed effects and baseline as a covariate was used for treatment group comparison. The LS mean of the treatment difference estimated from the model at Week 26 is provided.

Percentage and duration of time within a glucose range: The percentage of time within a specified glucose range (target, hypo- or hyperglycaemia ranges) was calculated as the number of observations within the specified range divided by the number of observations in the time interval (e.g., 24-hour period) on all valid CGM days at the same visit. The duration (in minutes) within the glucose range was calculated as the percentage of time within the glucose range times the length of the period (24-hour, 18 hour, and 6 hour, for the periods of 24-hour, daytime, or night-time, respectively). For a visit, the average percentage across all valid CGM days during the visit was calculated and used for the calculation of the duration (in minutes) of time in the specified range during the 24-hour period for this patient by multiplying the average percentage with 1440 minutes.

Post-Meal Dosing Comparison: LY900014+20 versus Humalog, when administered as prandial insulin (0 to 2 minutes prior to the start of a meal), **with regard to the $iAUC_{0\text{-}2\ hours}$** after the start of meals obtained from up to 10 days of CGM use at Week 26.

Time in Glucose Target Range: time in the glucose target range of 70 to 180 mg/dL [3.9 to 10.0 mmol/L] during daytime, normalized to 24-hour period at Week 26.

Average Glucose Excursions: postmeal average glucose excursions following all meals combined at Week 26 (0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours postmeal).

Ambulatory Glucose Profiles for Postprandial Glucose Control: mean ambulatory glucose profiles for postprandial glucose control at baseline and Week 26.

2.4.1.3.2. Results

A total of 88 patients were randomized after signing the ICF for the CGM addendum. Of the 88 randomized patients, 79 were included in the CGM analysis set (37 in the Humalog group, 29 in the LY900014 group and 13 in the LY900014+20 group). This is lower than the planned completion number of 130. The addendum with 130 patients had 80% power to detect a difference of 22 mg·h/dL in the postmeal $iAUC_{0\text{-}2\ hours}$ at Week 26, assuming an SD of 39.5 mg·h/dL. With only 79 patients, the addendum was not powered to detect this difference.

Detailed disposition of participants is not included in this AR for brevity. Of subjects randomised to the Humalog, LY900014, and LY900014+20 groups, respectively, 34/37, 27/29 and 13/13 subjects completed the study.

Baseline characteristics

Baseline characteristics for the addendum are given in Table 32. Age range was from 4 to 17 years, with 3 subjects <6 years of age and 18 subjects from 6 to 12 years of age.

Table 32 Baseline Characteristics in CGM Addendum

Parameter	Humalog (N = 37)	LY900014 (N = 29)	LY900014+20 (N = 13)	Total (N = 79)	P-value[a]
Sex, n (%)					
Female	17 (45.9)	14 (48.3)	7 (53.8)	38 (48.1)	0.886
Male	20 (54.1)	15 (51.7)	6 (46.2)	41 (51.9)	
Age (years)					
Mean (SD)	12.1 (3.3)	12.3 (3.7)	13.4 (2.9)	12.4 (3.4)	0.477
Minimum, maximum	4, 17	5, 17	6, 17	4, 17	
Age group (years), n (%)					
1 to <12	11 (29.7)	9 (31.0)	1 (7.7)	21 (26.6)	0.239
12 to <18	26 (70.3)	20 (69.0)	12 (92.3)	58 (73.4)	
1 to <6	2 (5.4)	1 (3.4)	0	3 (3.8)	0.534
6 to <12	9 (24.3)	8 (27.6)	1 (7.7)	18 (22.8)	
12 to <18	26 (70.3)	20 (69.0)	12 (92.3)	58 (73.4)	
Race, n (%)					
Asian	0	1 (3.4)	0	1 (1.3)	0.694
Black or African American	1 (2.7)	0	1 (7.7)	2 (2.5)	
Multiple	1 (2.7)	0	0	1 (1.3)	
Native Hawaiian or Other Pacific Islander	1 (2.7)	0	0	1 (1.3)	
Not Reported	1 (2.7)	0	0	1 (1.3)	
White	33 (89.2)	28 (96.6)	12 (92.3)	73 (92.4)	
Ethnicity, n (%)					
Hispanic or Latino	8 (21.6)	4 (13.8)	3 (23.1)	15 (19.0)	0.553
Not Hispanic or Latino	27 (73.0)	25 (86.2)	9 (69.2)	61 (77.2)	
Not Reported	2 (5.4)	0	1 (7.7)	3 (3.8)	
Country, n (%)					
Israel	1 (2.7)	0	0	1 (1.3)	0.988
Italy	4 (10.8)	3 (10.3)	1 (7.7)	8 (10.1)	
Poland	5 (13.5)	4 (13.8)	2 (15.4)	11 (3.9)	
Spain	7 (18.9)	4 (13.8)	2 (15.4)	13 (16.5)	
United States	20 (54.1)	18 (62.1)	8 (61.5)	46 (58.2)	
BMI (kg/m^2)					
Mean (SD)	20.38 (3.98)	21.25 (4.81)	22.01 (5.49)	20.98 (4.55)	0.473
Minimum, maximum	13.82, 31.21	14.39, 36.17	16.02, 37.30	13.82, 37.30	
Duration of diabetes (years)					
Mean (SD)	4.5 (3.25)	4.02 (3.63)	4.3 (3.4)	4.29 (3.38)	0.850
Minimum, maximum	0.5, 13.5	0.6, 12.1	0.7, 10.5	0.5, 13.5	
HbA1c, mean (SD)					
Study screening (%)	7.91 (0.80)	7.60 (0.83)	7.67 (0.88)	7.76 (0.83)	0.300
Study screening (mmol/mol)	62.97 (8.77)	59.61 (9.05)	60.32 (9.58)	61.30 (9.03)	
Baseline (%)	7.87 (0.91)	7.56 (0.75)	7.59 (0.84)	7.71 (0.85)	0.283
Baseline (mmol/mol)	62.55 (9.99)	59.12 (8.18)	59.48 (9.14)	60.79 (9.26)	
Basal insulin at randomization, n (%)					
Insulin degludec	12 (32.4)	8 (27.6)	3 (23.1)	23 (29.1)	0.823
Insulin detemir	2 (5.4)	3 (10.3)	2 (15.4)	7 (8.9)	
Insulin glargine	23 (62.2)	18 (62.1)	8 (61.5)	49 (62.0)	
Prandial insulin at screening, n (%)					
Insulin aspart	13 (35.1)	11 (37.9)	5 (38.5)	29 (36.7)	0.979
Insulin glulisine	2 (5.4)	1 (3.4)	1 (7.7)	4 (5.1)	
Insulin lispro U100	22 (59.5)	17 (58.6)	7 (53.8)	46 (58.2)	
Personal CGM use, n (%)					
Yes	23 (62.2)	20 (69.0)	7 (53.8)	50 (63.3)	0.631

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

[a] P-value for overall treatment effect.

Although 79 patients were included in the CGM analysis set, there were instances where meal occurrence time data were collected but did not contribute to analysis. Only subjects with nonmissing baseline values and at least 1 nonmissing postbaseline value for the response variable were included in analysis. Reasons for noninclusion include data collected on a nonvalid CGM day or postmeal CGM data collected was fewer

than 70% (i.e., 16 or less readings for 2-hour endpoints, etc.). The table 33 below shows patient data in the CGM analysis set that was eligible for endpoint analysis.

Table 33 Subjects eligible for analysis in CGM Addendum

Endpoints	Total (N = 79)
Day-based endpoints	
Both baseline and postbaseline	55
Baseline only	18
Postbaseline only	3
None	3
Meal-based endpoints	
Both baseline and postbaseline	40
Baseline only	19
Post-baseline only	7
None	13

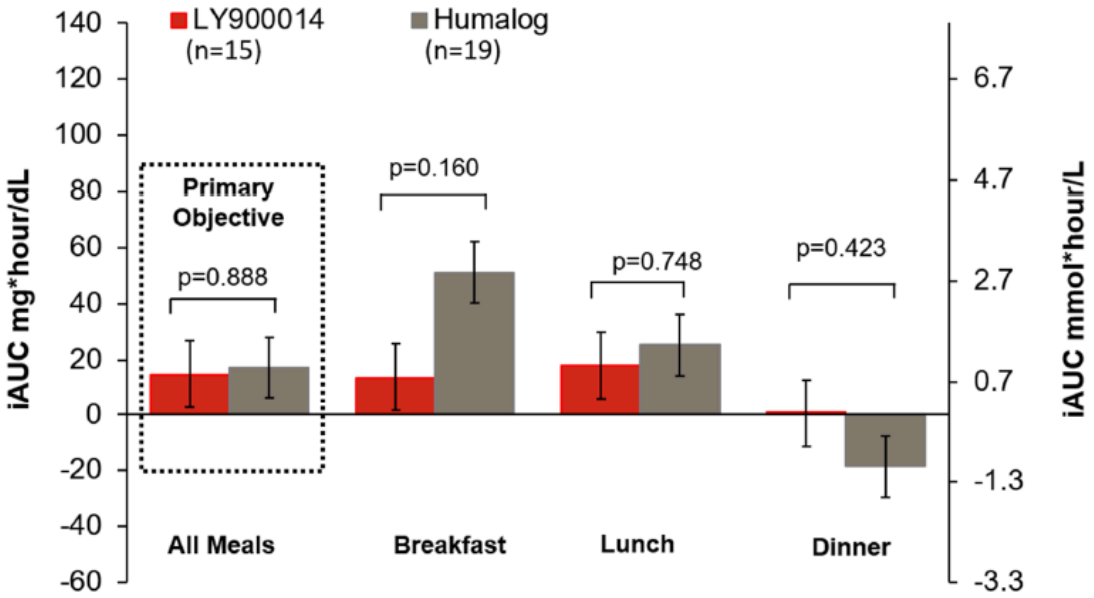
Abbreviation: N = number of subjects in the population.

Primary objective

Incremental $AUC_{0\text{-}2h}$ Humalog vs. LY900014

Figure 23 presents the results for the primary objective, comparison between LY900014 and Humalog, when administered as prandial insulin (0 to 2 minutes prior to the start of a meal), with regard to the $iAUC_{0\text{-}2\ hours}$ after the start of meals obtained from up to 10 days of CGM use at Week 26. The LSMean difference of −2.4 mg·h/dL (95% CI −36.2, 31.5) in the postmeal $iAUC_{0–2\ hours}$ at Week 26 was not nominally statistically significantly different between LY900014 and Humalog.

Figure 23 Incremental $AUC_{0\text{-}2\ hours}$ by meal at Week 26 for Humalog and LY900014.



Abbreviations: CGM = continuous glucose monitoring; iAUC = incremental area under the glucose versus time curve; LSM = least squares mean; n = number of subjects who recorded meal start times in CGM diary; SE = standard error.
Data are LSM (SE).

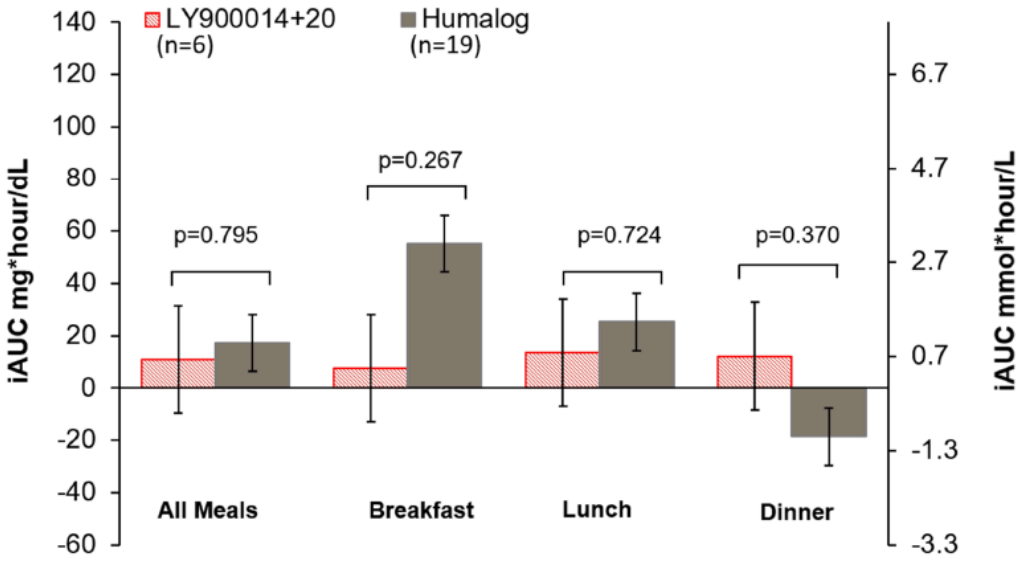
Note: ANCOVA model: $iAUC_{0\text{-}2\ hours}$ at Week 26 = $iAUC_{0\text{-}2\ hours}$ at baseline + Type of Basal Insulin at Randomization + Pooled Age Group 1 + HbA1c Stratum + Treatment.

Secondary objectives

Incremental $AUC_{0\text{-}2h}$ Humalog vs. LY900014+20

Results on the comparison of LY900014+20 and Humalog, with regard to the $iAUC_{0\text{-}2\ hours}$ after the start of meals obtained from up to 10 days of CGM use at Week 26 are presented in Figure 24. None of the noted differences were nominally statistically significant.

Figure 24 Incremental $AUC_{0\text{-}2\ hours}$ by meal at Week 26 for Humalog and LY900014+20.



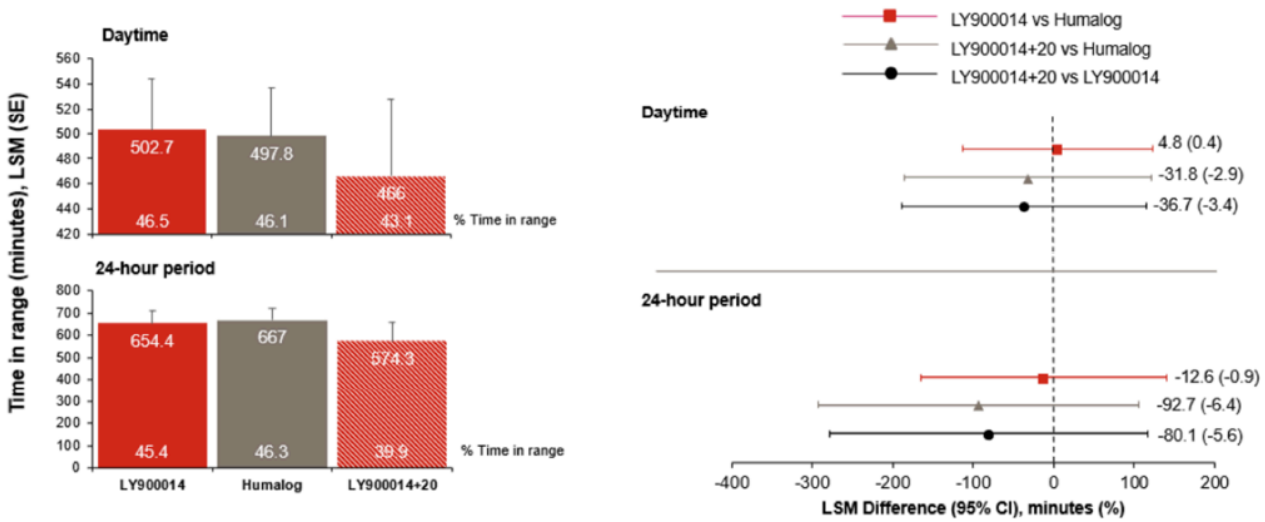
Abbreviations: CGM = continuous glucose monitoring; iAUC = incremental area under the glucose versus time curve; LSM = least squares mean; n = number of subjects who recorded meal start times in CGM diary; SE = standard error.
Data are LSM (SE).
Source: /lillyce/prd/ly900014/i8b_mc_itsb/final/output/shared/smcgi01.rtf

Note: ANCOVA model: $iAUC_{0\text{-}2\ hours}$ at Week 26 = $iAUC_{0\text{-}2\ hours}$ at baseline + Type of Basal Insulin at Randomization + Pooled Age Group 1 + HbA1c Stratum + Treatment.

Time in Glucose Target Range

No nominally statistically significant differences were observed in time in glucose range 3.9 to 10.0 mmol/L (70 to 180 mg/dL). Mean time spent in target range was below 50% in all study groups.

Figure 25 Time in glucose target range (3.9 to 10.0 mmol/L [70 to 180 mg/dL]) at Week 26.



Abbreviations: CI = confidence interval; LSM = least squares mean; SE = standard error; vs = versus.
Source: /lillyce/prd/ly900014/i8b_mc_itsb/final/output/shared/smcgd01

Note: ANCOVA model for duration/percentage of endpoint measures = Baseline value + Type of Basal Insulin at Randomization + Pooled Age Group 1 + HbA1c Stratum + Treatment.

Average glucose excursions

Average glucose excursions at Week 26 from 0 to 1 hour postmeal for all meals combined were only analysed for the subset of completers who recorded meal start times in their CGM diary (Humalog [n = 19]; LY900014 [n = 15]; LY900014+20 [n = 6]) (Table 34). No differences were observed for the average glucose excursions combined for all meals. The only nominally statistically significant findings in this small subset were lower glucose excursions from premeal to 3 and to 4 hours postmeal for breakfast in the LY9000014 group vs. Humalog at Week 26 (data not shown for brevity).

Table 34 Summary and Analysis of Average Glucose Excursions at Week 26

Time Point	Unit	Treatment Group	n	LSM (SE)	LSM Difference at Week 26 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
0 to 1 hour postmeal for all meals combined	mg/dL	Humalog	19	6.21 (4.301)	A: 0.12 (-13.29,13.53), 0.985
		LY900014	15	6.34 (4.764)	B: -0.24 (-19.60, 19.12), 0.980
		LY900014+20	6	5.98 (8.073)	C: -0.36 (-19.63,18.91), 0.970
	mmol/L	Humalog	19	0.35 (0.239)	A: 0.01 (-0.74, 0.75), 0.985
		LY900014	15	0.35 (0.265)	B: -0.01 (-1.09, 1.06), 0.980
		LY900014+20	6	0.33 (0.448)	C: -0.02 (-1.09, 1.05), 0.970
0 to 2 hours postmeal for all meals combined	mg/dL	Humalog	19	8.39 (5.350)	A: -1.26 (-17.91, 15.40), 0.879
		LY900014	15	7.13 (5.916)	B: -3.28 (-27.43, 20.88), 0.784
		LY900014+20	6	5.11 (10.061)	C: -2.02 (-26.00, 21.96), 0.865
	mmol/L	Humalog	19	0.47 (0.297)	A: -0.07 (-1.00, 0.86), 0.879
		LY900014	15	0.40 (0.329)	B: -0.18 (-1.52, 1.16), 0.784
		LY900014+20	6	0.28 (0.559)	C: -0.11 (-1.44, 1.22), 0.865
0 to 3 hours postmeal for all meals combined	mg/dL	Humalog	19	9.55 (5.535)	A: -2.91 (-20.15,14.32), 0.733
		LY900014	15	6.64 (6.125)	B: -5.69 (-30.65, 19.28), 0.646
		LY900014+20	6	3.87 (10.406)	C: -2.77 (-27.59, 22.04), 0.821
	mmol/L	Humalog	19	0.53 (0.307)	A: -0.16 (-1.12, 0.80), 0.733
		LY900014	15	0.37 (0.340)	B: -0.32 (-1.70, 1.07), 0.646
		LY900014+20	6	0.21 (0.578)	C: -0.15 (-1.53, 1.22), 0.821
0 to 4 hours postmeal for all meals combined	mg/dL	Humalog	19	12.46 (5.445)	A: -4.33 (-21.34, 12.67), 0.607
		LY900014	15	8.12 (6.031)	B: -5.52 (-30.01, 18.97), 0.649
		LY900014+20	6	6.93 (10.202)	C: -1.19 (-25.54, 23.16), 0.921
	mmol/L	Humalog	19	0.69 (0.302)	A: -0.24 (-1.19, 0.70), 0.607
		LY900014	15	0.45 (0.335)	B: -0.31 (-1.67, 1.05), 0.649
		LY900014+20	6	0.39 (0.567)	C: -0.07 (-1.42, 1.29), 0.921

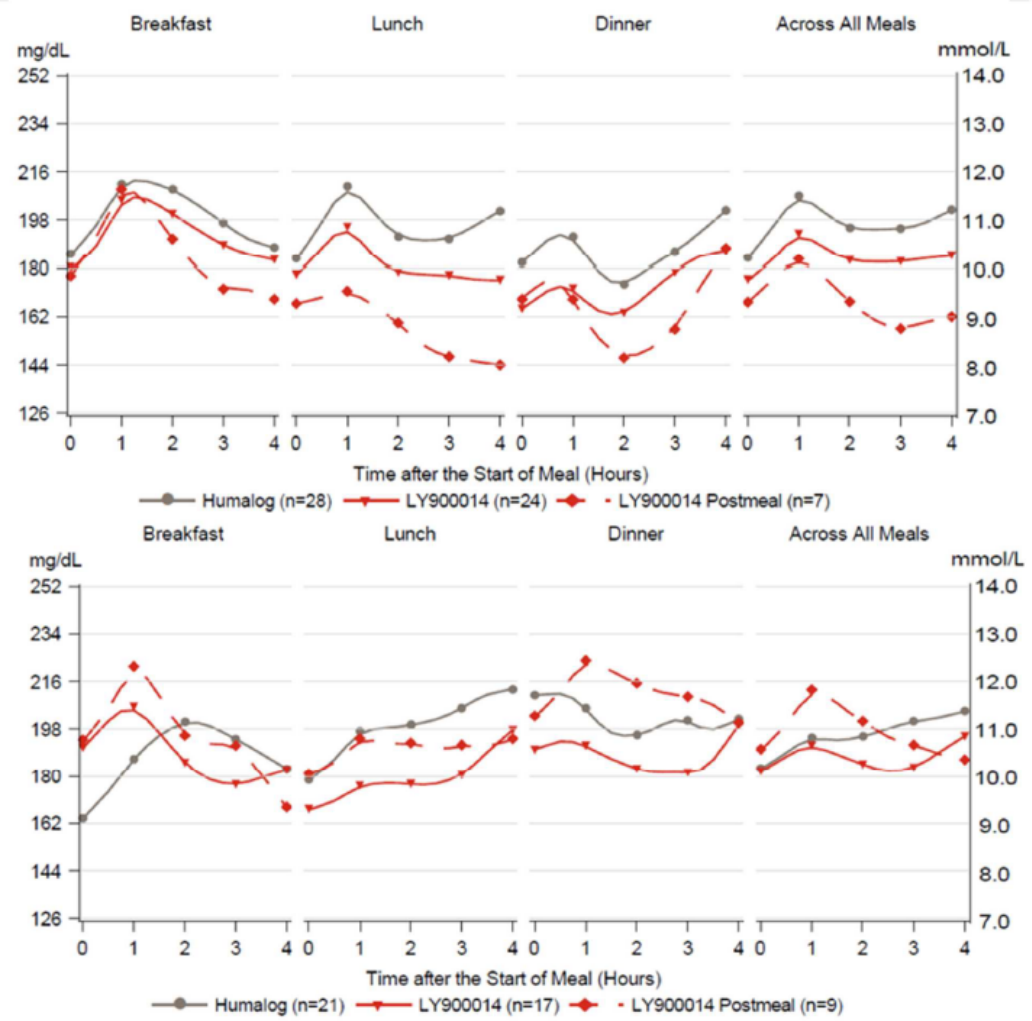
Abbreviations: CI = confidence interval; LSM = least-squares mean; n = number of subjects who recorded meal start times in CGM diary; SE = standard error; vs = versus.

Note: Only subjects with nonmissing baseline value and at least 1 nonmissing postbaseline value of the response variable were included in analysis.

Ambulatory Glucose Profiles for Postprandial Glucose Control

Ambulatory glucose profiles for postprandial glucose control are presented in Figure 26. No formal statistical analyses were performed on these profiles.

Figure 26 Ambulatory glucose profiles for postprandial glucose control at baseline (top pane) and at Week 26 (bottom pane)



Abbreviations: CGM = continuous glucose monitoring; vs = versus.
Note: vs time postmeal of glucose means calculated across patient-level means at 15-minute intervals for all valid CGM days.
0 hour mean is calculated as the average of the CGM values in the time window [-19, 0] mins relative to the start of the meal.
Glucose mean curves are calculated from the locally weighted polynomial regression (0.30 smoothing).
Source: /lillyce/prd/ly900014/i8b_mc_itsb/final/output/shared/gragp03.rtf; gragp04.rtf

For results on time in hypoglycaemic and hyperglycaemic ranges, see Section 2.5.5 of this AR.

Glucose Variability

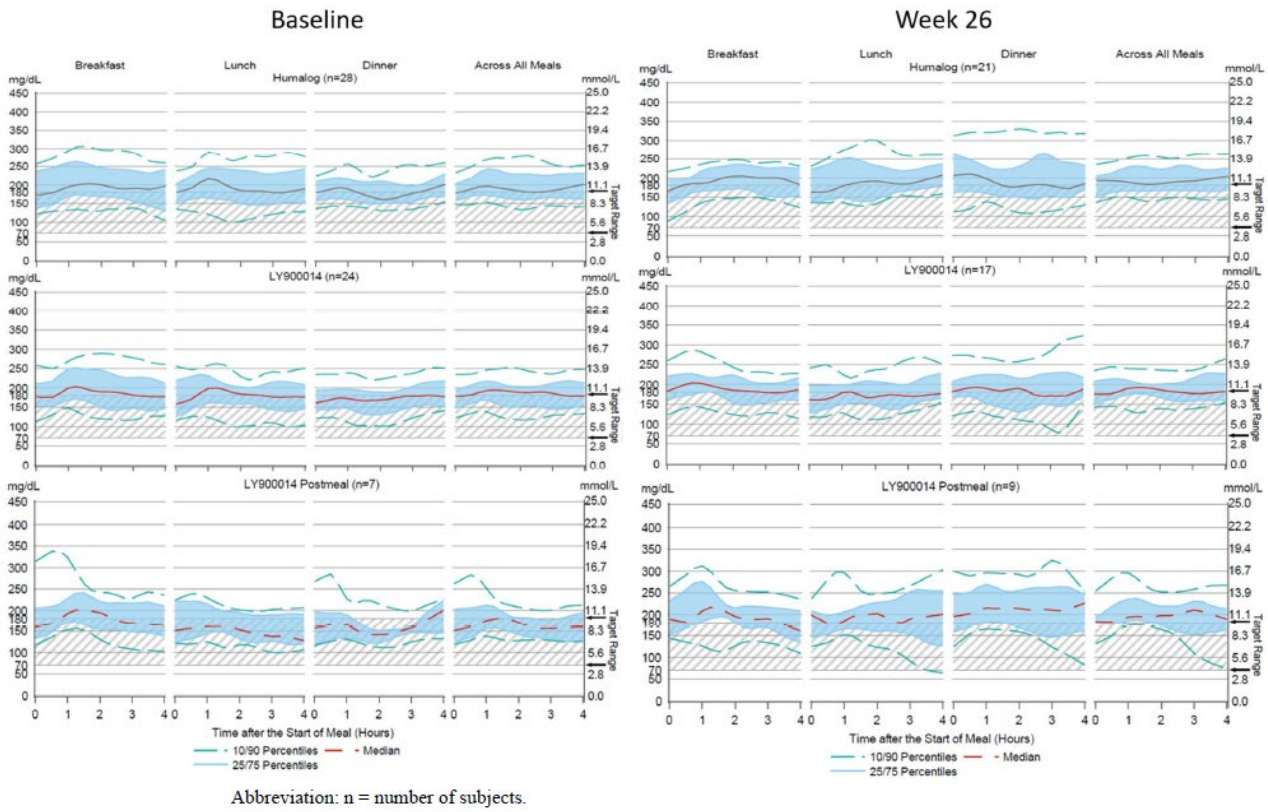
Ambulatory glucose profiles during the 4-hour period after meals as represented by median, 25th/75th percentiles, and 10th/90th percentiles are shown at baseline when all patients were treated with Humalog, and at the 26-week assessment by treatment assignment (Figure 27).

Upon visual inspection, LY900014 and Humalog postprandial glucose patterns were similar between both treatment groups at each time interval at each meal and across all meals, suggesting small differences in glucose variability. For all 3 treatment groups, there appears to be increased variability at 26 weeks compared with baseline in the post-dinner glucose profiles. In the LY900014+20 group, there is greater

variability observed from baseline to Week 26 compared with LY900014 and Humalog, with an increase noted at 1 hour (morning, midday) and across all meals and a tendency toward hypoglycaemia at 4 hours (midday and dinner) and across all meals.

Interpretation of data and its clinical importance is limited by the small number of participants with evaluable data due to missing mealtimes in the patient diary.

Figure 27 Postprandial ambulatory glucose profiles at baseline and Week 26



Abbreviation: n = number of subjects.

No differences were observed in *within-day glycaemic variability* between treatment groups (data not shown for brevity).

The MAH claims that between-day glucose variability between LY900014 and Humalog at Week 26 showed nominally statistically significantly lower mean of daily differences (MODD) for the daytime, night-time, and 24-hour period; however, the opposite is true (table 35). Furthermore, according to the MAH, LY900014+20 versus Humalog at Week 26 resulted in statistically significantly lower MODD for the night-time and 24-hour period but this is incorrect, too, since postmeal administration resulted in nominally statistically significantly greater between-day variation compared to Humalog (table 35).

Table 35 Between-Day Glycaemic Variability - Daytime, Night-time, 24-Hour Period, Mean of Daily Differences at Week 26

Variable Analyzed: Mean of Daily Differences (mg/dL) (Daytime)

		Actual Value					Change from Baseline					
Time Point / Treatment	n	Mean (SD)	Min	Median	Max	LSMean (SE)*a*b	Mean (SD)	Min	Median	Max	LSMean (SE)*a	Within treatment p-value*a
Week 26 (Visit 15)												
Humalog	24	75.7 (17.43)	44.3	77.3	107.1	74.9 (2.88)	4.1 (14.43)	-22.0	5.1	29.1	2.5 (2.88)	0.389
LY900014	20	82.8 (18.78)	48.9	84.8	111.9	84.2 (3.10)	12.1 (12.20)	-5.1	10.4	33.4	11.8 (3.10)	<.001
LY900014 Postmeal	10	85.0 (23.28)	43.0	85.9	125.5	83.9 (4.56)	7.0 (18.71)	-25.0	13.9	29.3	11.5 (4.56)	0.016

Pairwise Comparison	LSMean Change Difference*a*b	95% CI for Difference*a*b	p-value *a*b
LY900014 vs Humalog	9.3	(0.6,18.0)	0.036
LY900014 Postmeal vs Humalog	9.0	(-2.2,20.1)	0.114
LY900014 Postmeal vs LY900014	-0.4	(-11.5,10.8)	0.949

Variable Analyzed: Mean of Daily Differences (mg/dL) (Night-time)

		Actual Value					Change from Baseline					
Time Point / Treatment	n	Mean (SD)	Min	Median	Max	LSMean (SE)*a*b	Mean (SD)	Min	Median	Max	LSMean (SE)*a	Within treatment p-value*a
Week 26 (Visit 15)												
Humalog	24	70.9 (19.89)	25.8	67.8	112.5	68.5 (5.92)	-4.0 (29.12)	-65.1	-10.4	42.3	-7.9 (5.92)	0.189
LY900014	19	87.9 (39.87)	16.5	85.3	189.0	87.2 (6.61)	10.2 (37.55)	-64.0	2.0	92.2	10.7 (6.61)	0.112
LY900014 Postmeal	10	94.8 (40.16)	30.7	87.0	171.7	101.9 (9.41)	17.2 (31.46)	-15.1	14.8	68.2	25.5 (9.41)	0.009

Pairwise Comparison	LSMean Change Difference*a*b	95% CI for Difference*a*b	p-value *a*b
LY900014 vs Humalog	18.6	(0.5,36.8)	0.045
LY900014 Postmeal vs Humalog	33.4	(10.5,56.3)	0.005
LY900014 Postmeal vs LY900014	14.8	(-8.6,38.2)	0.209

Variable Analyzed: Mean of Daily Differences (mg/dL) (24-Hour)

		Actual Value					Change from Baseline					
Time Point / Treatment	n	Mean (SD)	Min	Median	Max	LSMean (SE)*a*b	Mean (SD)	Min	Median	Max	LSMean (SE)*a	Within treatment p-value*a
Week 26 (Visit 15)												
Humalog	24	74.1 (16.16)	45.9	73.1	103.9	73.0 (3.40)	1.5 (16.45)	-29.5	-1.8	30.3	-0.4 (3.40)	0.896
LY900014	20	83.3 (20.51)	39.6	87.6	114.1	84.1 (3.67)	10.9 (15.81)	-19.8	8.4	40.0	10.6 (3.67)	0.006
LY900014 Postmeal	10	89.6 (30.76)	40.0	85.9	158.8	90.7 (5.38)	11.8 (23.27)	-23.8	6.8	61.4	17.2 (5.38)	0.003

Pairwise Comparison	LSMean Change Difference*a*b	95% CI for Difference*a*b	p-value *a*b
LY900014 vs Humalog	11.1	(0.8,21.3)	0.035
LY900014 Postmeal vs Humalog	17.6	(4.5,30.8)	0.010
LY900014 Postmeal vs LY900014	6.6	(-6.6,19.7)	0.320

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CGM = continuous glucose monitoring; CI = confidence interval; IP =investigational product; LSMean = least squares mean; LY900014 Postmeal = LY900014 administered as postprandial insulin up to 20 minutes after the start; Max = maximum; Min = minimum; n = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

Note 1: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
Note 2: IP = investigational product

*a - ANCOVA model for endpoint measures: Variable = Baseline + Type of Basal Insulin at Randomization + Pooled Age Group 1 + HbA1c Stratum + Treatment (Type III sum of squares).
*b - ANOVA model for baseline measures: Variable = Treatment (Type III sum of squares).

There were no other nominally statistically significant differences observed between the LY900014, LY900014+20, and Humalog groups for any other secondary objective.

2.4.2. Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

36 Summary of Efficacy for trial I8B-MC-ITSB

<table>
<tr><td colspan="4">Title: A Prospective, Randomised, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes: PRONTO-Peds</td></tr>
<tr><td>Study Identifier</td><td colspan="3">I8B-MC-ITSB
EUDRA CT: 2018-002371-18</td></tr>
<tr><td rowspan="5">Design</td><td colspan="3">Phase 3, prospective, randomised, outpatient, multinational, multicentre, parallel, active-controlled study conducted in children and
adolescent patients with T1D currently using an MDI regimen</td></tr>
<tr><td colspan="2">Duration of Screening:</td><td>1 week</td></tr>
<tr><td colspan="2">Duration of Lead-in Period:</td><td>4 weeks</td></tr>
<tr><td colspan="2">Duration of Treatment Period:</td><td>26 weeks</td></tr>
<tr><td colspan="2">Follow-up Period:</td><td>2 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="3">The primary objective of this study was to test the hypothesis that LY900014 is noninferior to Humalog on glycaemic control (NIM=0.4% for HbA1c) in patients 1 to <18 years of age with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal) in combination with basal insulin as part of an MDI regimen for 26 weeks.</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 to 2 minutes before the start of the meal (mealtime) in combination with basal insulin (insulin glargine, insulin detemir, or insulin degludec). Individualised dosing titrated to achieve glycaemic targets.
Randomised: LY900014 (N = 280); Humalog (N = 298)</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, insulin detemir, or insulin degludec). Individualised dosing titrated to achieve glycaemic targets. Randomised: LY900014+20 (N = 138)</td></tr>
<tr><td rowspan="3">Endpoints and Definitions</td><td rowspan="2">Multiplicity-Controlled 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 glycaemic control (NIM=0.4% for HbA1c) when administered 20 minutes after the start of a meal (LY900014+20) (Objective 1). An NIM of 0.3% was also tested.</td></tr>
<tr><td>Change in HbA1c (%) from baseline to Week 26</td><td>To test the hypothesis that LY900014 is superior to Humalog in improving glycaemic control (HbA1c) when administered as prandial insulin (0 to 2 minutes prior to the meal) (Objective 2).</td></tr>
<tr><td colspan="2">Other Efficacy Measures</td><td>SMBG, Insulin dose, Pediatric Quality of Life</td></tr>
<tr><td>Database Lock Date</td><td colspan="3">16 July 2021</td></tr>
<tr><td colspan="4">Results and Analysis</td></tr>
</table>

Analysis Population and Time Point Description	**Primary Efficacy Analysis and Multiplicity-Controlled Secondary Objectives** The efficacy estimand included data collected prior to permanent discontinuation of study treatment. The ITT estimand included all data collected regardless of study drug use. The efficacy estimand was the primary estimand for the EU submission. HbA1c: Change from baseline to Week 26
Analysis Description	**Control for Multiplicity:** A hierarchical approach for multiple comparisons 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-controlled secondary objectives. **Primary Efficacy Analyses**: An MMRM analysis of data from all randomised patients, collected prior to permanent discontinuation of study treatment (efficacy estimand), was used to analyse the primary efficacy measure. 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 were also conducted. **Multiplicity-Controlled Secondary Objectives** included (Objective 1) noninferiority of LY900014+20 to Humalog for change from baseline in HbA1c (Objective 2) superiority of LY900014 to Humalog for change from baseline in HbA1c
Results	**Primary Objective: All Randomised Patients, Efficacy Estimand** The primary objective 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 -0.02% (-0.23 mmol/mol), with a 2-sided 95% CI of -0.17% to 0.13% (-1.84 mmol/mol to 1.39 mmol/mol). **Multiplicity-Controlled Secondary Objectives: All Randomised Patients, Efficacy Estimand** Multiplicity-adjusted secondary objective 1 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 margins of 0.4% and 0.3%. • LSM difference between treatments (LY900014+20 minus Humalog) was -0.02% (-0.17 mmol/mol), with a 2-sided 95% CI of -0.20% to 0.17% (-2.15 mmol/mol to 1.81 mmol/mol).

Results (continued)

Multiplicity-adjusted secondary objective 2 was not achieved. LY900014 was not superior to Humalog for glycaemic control.

- LSM difference between treatments (LY900014 minus Humalog) was -0.02% (-0.23 mmol/mol), with a 2-sided 95% CI of -0.17% to 0.13% (-1.84 mmol/mol to 1.39 mmol/mol).

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

For the primary objective and all multiplicity-adjusted secondary objectives, the results were consistent between the efficacy and the ITT estimand.

Sensitivity Analysis
Sensitivity analyses for both the efficacy and ITT estimands were consistent with the findings of the primary analyses.

Summary and Analysis of HbA1c at Baseline and Week 26 All Randomised Patients, Efficacy Estimand

	LSM (SE)			LSM Difference at Week 26
Treatment Group	**Baseline**	**Week 26**	**Change from Baseline at Week 26**	**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**
HbA1c (mmol/mol)				
Humalog	61.84 (0.56)	62.57 (0.57)	0.94 (0.57)	A: -0.23 (-1.84, 1.39), p=0.783 B: -0.17 (-2.15, 1.81), p=0.867 C: 0.06 (-1.95, 2.06), p=0.956
LY900014	61.57 (0.58)	62.35 (0.59)	0.71 (0.59)	
LY900014+20	61.38 (0.82)	62.41 (0.83)	0.77 (0.83)	
HbA1c (%)				
Humalog	7.81 (0.05)	7.88 (0.05)	0.09 (0.05)	A: -0.02 (-0.17, 0.13), p=0.783 B: -0.02 (-0.20, 0.17), p=0.867 C: 0.01 (-0.18, 0.19), p=0.956
LY900014	7.78 (0.05)	7.85 (0.05)	0.06 (0.05)	
LY900014+20	7.77 (0.07)	7.86 (0.08)	0.07 (0.08)	

Results (continued)	**Lead-in Period** There was a clinically significant improvement in HbA1c in all treatment groups during the lead-in period designed to optimise basal insulin therapy. **From Baseline to Week 26** **Mealtime LY900014 compared to Mealtime Humalog**: HbA1c remained steady 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-controlled objective 1 (change from baseline in HbA1c), HbA1c remained steady from baseline in both treatment groups. Noninferiority was confirmed for HbA1c change from baseline with LY900014+20 compared to Humalog. **LY900014+20 compared to Mealtime LY900014**: At 26 weeks, HbA1c was similar between the mealtime LY900014 and postmeal LY900014 group.
	Other Efficacy Measures
	SMBG: BG at Week 26 LY900014 compared to Humalog: SMBG was lower at morning 1-hour postmeal, evening 1-hour postmeal, and for the 1-hour postmeal daily mean. **PPG Excursions from Premeal to 1-hour Postmeal Daily Mean, Week 26** LY900014 compared to Humalog: lower excursions with LY900014 LY900014+20 compared to LY900014: higher with LY900014+20
	Insulin Dose At Week 26 basal, bolus, and total insulin doses were not different between treatments.
	Paediatric Quality of Life At the LOCF endpoint, PedsQL scores were not different between treatments.

Abbreviations: BG = blood glucose; CI = confidence interval; HbA1c = haemoglobin A1c; ITT = intent to treat; LOCF = last observation carried forward; LSM = least-square mean; MDI = multiple daily injection; MMRM = mixed-model repeated measures; N = number of patients; NIM = noninferiority margin; PedsQL = Pediatric Quality of Life; PPG = postprandial glucose; SE = standard error; SMBG = self-monitored blood glucose; T1D = type 1 diabetes.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Paediatric development

In 2016, the CHMP recommended that a clinical efficacy and safety study should be conducted for paediatric patients, instead of only PK studies, even if the PK profile would be similar in adults and paediatric patients. This advice was followed by the MAH, and one pivotal Phase 3 study, I8B-MC-ITSB (ITSB), was conducted for children and adolescents with T1D. A clinical pharmacology study, I8B-MC- ITSA (ITSA), established the PK/PD profile during a test meal of Lyumjev and Humalog following a single subcutaneous bolus dose administered through injection or CSII in paediatric and adult patients with T1D. ITSA was previously reviewed (EMEA/H/C/005037/II/0005). The current application for indication of use of Lyumjev in subjects aged 1 year and above is based on ITSB and on PK modelling based on ITSA.

ITSB methods

The study ITSB is considered appropriately designed. The primary objective was to test the hypothesis that LY900014 is noninferior to Humalog for glycaemic control (change from baseline in HbA1c), when both are administered preprandially (0−2 minutes before meal). These study arms were blinded. Subjects in the third study arm administered LY900014 postprandially up to 20 minutes. Obviously, administration time could not be blinded; however, the sponsor remained blinded for all treatment groups. There were two gated objectives: 1) to test the hypothesis that LY900014 administered within 20 minutes after the meal is noninferior to Humalog administered 0 to 2 minutes prior to the meal in change from baseline in HbA1c; and 2) to test the hypothesis that LY900014 is superior to Humalog in improving glycaemic control (change from baseline in HbA1c) when both are administered preprandially. The noninferiority margin was 0.4% for the FDA, and 0.3% for the EU, in line 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). Hence, the relevant NIM in the current assessment for the primary endpoint is 0.3% (3 mmol/mol).

The number of stratification factors exceeds the recommended number of ICH guideline E9 Statistical Principles for Clinical Trials. The number of patients randomised must have been very small in a considerable proportion of strata. As such it is questionable whether the randomisation procedure was optimal in ensuring balanced treatment groups with respect to the key factors. However, given that this randomisation actually resulted in good balance with respect each of the stratification factors, this potential methodological risk can be ignored.

The first patient visit (FPV) of ITSB occurred on 26 Oct 2018. Both of the two amendments to the protocol are dated after the FPV: version ITSB(a) on 18 Nov 2019 and version ITSB(b) on 30 Apr 2020. However. these amendments are considered nonsubstantial. ITSB(a) e.g., allowed use of personal CGM/FGM, more flexibility to glucose monitoring and requirement to confirm any suspected hypoglycaemia events by BG meter. ITSB Amendment (b) included, e.g., changes in daily insulin dose range for younger and active children and adolescents; rescreen of patients with prior screen fail or discontinuation due to COVID-19 enrolment pause. Protocol deviations are also considered not to have relevantly affected study results.

The duration of the study, with a 1-week screening, 4-week lead-in period, 26-week treatment period and 2-week safety follow-up period is regarded sufficient. Inclusion and exclusion criteria were usual for studies in paediatric subjects with T1D. Glycaemic targets and monitoring of glucose values were appropriate. Secondary efficacy and safety endpoints were also usual for a T1D trial.

The key assessments of efficacy and the corresponding statistical analyses of these were fit for purpose. Specifically, the efficacy estimand, largely corresponding to the hypothetical HbA1b outcomes *as if* all

randomised subjects completed the study is considered adequate approach for comparing the outcomes between the treatment groups for non-inferiority and is in accordance with relevant EMA guideline. The corresponding ITT analysis is considered supportive. The concordance of the two analytical approach and the robustness of each analyses are high because few subjects discontinued the study prematurely (see below).

Of minor note, care must be taken when interpreting the odds ratios for achieving target HbA1c levels between treatment groups as these are conditional odds ratios (on the covariates) rather than marginal. Furthermore, the documentation refers to the statistical method as generalized linear mixed model - suggesting that a subject-specific model may have been used - while the reference to unstructured covariance matrix suggest that a generalised estimating equation model was applied. Given the low importance of the odds ratio estimates in question, these points are not considered to require clarification.

Conduct of ITSB

Conduct of the study was overall acceptable. A total of 78 participants (10.9%) had at least 1 important protocol deviation, most commonly related to IP treatment assignment/randomisation error due to IWRS entry errors impacting stratification (n=24 [3.4%]), informed consent (n=22 [3.1%]), and study procedures (n=22 [3.1%]). Seven subjects were misinterpreted to not being female patients of childbearing potential and hence had missing pregnancy tests. Several patients changed visits to phone calls due to COVID-19 pandemic and missed some patient characteristics or values for the visit. Important protocol deviations were reviewed by the assessor and deemed not to have a relevant effect on the study results.

Approximately 96% of patients across treatment groups completed the study while on study drug.

ITSB substudies

There were two substudies of ITSB: one for assessment of HRQoL by PedsQL in an English-speaking subset of patients and another, the CGM Addendum, investigating glucose excursions over 24 hours. Documentation on these appendices of ITSB is not complete in the variation submission. Protocols, statistical analysis plans and other relevant documents of these substudies were received upon request.

In the CGM addendum study report, the MAH stated each hypothesis (comparisons between treatment groups) as being or not being statistically significant based on the nominal p-value. However, there was no control for study-wise type 1 error probability. Furthermore, in rapporteur's view, since the CGM addendum represents a substudy of ITSB, a strategy to control of type 1 error probability at the level as part of ITSB study should have been adopted. The rapporteur therefore chose to refer to each result as being or not being nominally statistically significant in this AR based on the p-value provided, and these results should not be considered as confirmation of a true difference in the target population. The number of participants in the CGM substudy was considerably lower than planned, and therefore the results from this substudy were bound to be inconclusive.

Efficacy data and additional analyses

ITSB

A total of 716 subjects participated, allocated to Humalog (n=298), preprandial LY900014 (n=280) or postprandial LY900014 (n=138). The groups were comparable at baseline. The numbers of subjects in each age group are deemed sufficient for granting indication for use. In total 253 subjects aged <12 years and 463 subjects aged 12 to <18 years were enrolled. There were only 27 subjects aged 3 to <6 years, of whom 10 in the LY900014 group and 10 in the LY900014 group. None were <3 years of age. Hence, the data on the youngest age group is scarce. The patients had a mean baseline HbA1c of 7.8% (61.8 mmol/mol) and a mean duration of diabetes of 4.6 years.

During the 4-week lead-in period, all patients taking other prandial insulins at screening switched to Humalog while remaining on their basal insulin regimen (insulin glargine, insulin detemir, or insulin degludec) throughout the study. During the lead-in, emphasis in insulin titration was on basal insulin adjustment. Prandial insulin was planned to be titrated to achieve optimal dosing during the first 12 weeks. Figure 28 shows that HbA1c did not markedly change in the Humalog group during the 26-week controlled period, whereas in both study arms using LY900014 an initial increase in HbA1c is seen during the 26-week comparative phase of the trial up to 12 weeks; even though the differences between treatment groups were small at any visit. During the latter part of the comparative phase, HbA1c decreased and was at 26 weeks similar in all three study arms. This phenomenon probably reflects caution in adjusting prandial insulin after switching from Humalog to IP. Finding optimal dosage of in the LY900014 and LY900014+20 arms seems to have taken the entire study duration, 26 weeks, instead of the planned 12 weeks. At Week 26, however, no statistical differences were seen in either total, basal or prandial insulin doses between study groups.

The study met its primary endpoint, non-inferiority of LY900014 to Humalog also with the relevant NIM for EU, 0.3% (3 mmol/mol). The primary objective of noninferiority of LY900014 versus Humalog in change from baseline in HbA1c at Week 26 was demonstrated for both the efficacy estimand and ITT estimand (efficacy estimand: LSM Difference [95% CI] = -0.02 [-0.17, 0.13]; ITT estimand: LSM Difference [95% CI] = -0.01 [-0.15, 0.14]). It is noteworthy that no improvement in mean glycaemic control was observed from baseline to 26 weeks in any treatment arm. Mean HbA1c (%/mmol/mol) at Week 26 was 7.88/62.57, 7.85/62.35 and 7.86/62.41 in the Humalog, LY900014, and LY900014+20 groups, respectively (efficacy estimand).

There were two multiplicity-controlled endpoints. Of these, superiority of LY900014 vs. Humalog in controlling glycaemia (change in HbA1c from baseline) was not met. Administering LY900014 within 20 minutes from start of meal was demonstrated noninferior to Humalog administered within 0-2 minutes before meal.

As expected, due to accelerated time-action profile, LY900014 reduced postprandial glucose (PPG) levels as measured by a 7-point SMBG profile. Notably, these analyses were not controlled for multiplicity. At Week 26, the difference between LY900014 and Humalog was in favour of Lyumjev from premeal to 1-hour postmeal actual glucose excursions at breakfast and at dinner (figures 5.4.2.2.6.2 and 5.4.2.2.6.3), however, the dinner premeal glucose were higher in those using mealtime LY900014. The change from baseline in the daily mean PPG excursion was −0.6 mmol/L (−11.3 mg/dL) with LY900014 compared to 0.1 mmol/L (1.9 mg/dL) with Humalog. The actual daily average of 1-hour PPG excursions (over all meals) was 0.8 mmol/L (13.2 mg/dL) higher at week 26 in the Humalog group than the LY900014 group.

The accelerated time-action profile of LY900014 also allowed patients to achieve similar glycaemic control (HbA1c) with postmeal dosing (up to 20 minutes after the start of the meal) as premeal dosing (administered 0 to 2 minutes before the start of the meal). The option to dose mealtime insulin postprandially is particularly important for paediatric patients for whom predicting the carbohydrate content of a meal is not always possible. However, the improvement in PPG values (change from baseline [CFB] in PPG excursions) was smaller when LY900014 was dosed after the meal: CFB of daily mean glucose excursion from premeal to 1-hour postmeal was −0.1 mmol/L (−2.5 mg/dL) for the LY900014+20 group vs. −0.6 mmol/L (−11.3 mg/dL) for the LY900014 group. The actual 1-hour postmeal excursion daily mean at Week 26 was for LY900014+20 vs. LY900014, in mmol/L (mg/dL), 0.3 (5.9) vs. −0.2 (−3.0), respectively. Hence, the PPG results favour premeal administration. Nevertheless, it should be noted that these results are not controlled for multiplicity and are as such not statistically robust, even though the MAH presents in the CSR p-values for the comparisons. Furthermore, since no difference in HbA1c was observed between premeal and postmeal administration, postmeal administration is considered an acceptable option when needed, e.g., when the carbohydrate content of the meal is not known before meal, similarly as has been approved in adults, and as approved for all age groups using Humalog.

The number of patients in the age group 3 to <6 years (n = 27) was small compared with the 6 to <12 years group (n = 226) and the 12 to <18 years group (n = 463). It is also notable that no subjects <3 years of age were included in ITSB. Altogether, there were only 5 subjects aged 3 years (1 in the Humalog, 4 in the LY900014 and none in the LY900014+20 group); 7 subjects aged 4 years (1 in the Humalog, 2 in the LY900014 and 4 in the LY900014+20 group); and 15 subjects aged 5 years (5 in the Humalog, 4 in the LY900014 and 6 in the LY900014+20 group). Hence, the efficacy data in the youngest age group are very limited. The MAH states that there were no significant treatment-by-subgroup interactions for age with actual HbA1c and HbA1c change from baseline, thus indicating no differential treatment effect of age on HbA1c. In the response to questions from prior assessment round, the MAH nevertheless informed that the for patients 3 to less than 6 years of age, there was a greater HbA1c reduction for LY900014 and LY900014+20 groups compared to the Humalog group (LY900014 - Humalog: −0.77% and LY900014+20 - Humalog: −0.46%). This could be interpreted to indicate increased efficacy at some time point after meals in smaller children, especially since part of the noted increase in hypoglycaemic event rate in subjects aged 3 to 6 years was according to the MAH's response to the LoQ due to a larger decrease in HbA1c in this age group. Nevertheless, the timing of the hypoglycaemic events was not accordant with the faster action profile of LY900014. The achieved mean HbA1c (SD) in children aged 3 to 6 years was furthermore very similar between the Humalog (N=10) and LY900014 (N=10) groups: 8.0% (0.7) and 7.9% (0.6), respectively. In the LY900014+20 group (N=7), the mean achieved HbA1c was somewhat lower: 7.6% (0.6). The change from baseline in HbA1c levels at Week 26 for patients 6 to less than 12 years of age and 12 to less than 18 years of age groups was similar across all treatment groups.

There is no pharmacological reason to assume different PD effect in the youngest children as opposed to older subjects. As a conclusion, extrapolation of efficacy data from older children to subjects aged 1 to 3 year is deemed acceptable.

Type 2 diabetes

No clinical efficacy and safety trials were conducted with Lyumjev in paediatric patients with T2D. Even though the incidence in T2D is increasing, it remains rare in European children and adolescents and only occurs from age of 10 years onwards. T2D is largely treated by other medications and lifestyle measures in paediatric patients; however, some of these patients need insulin for control of hyperglycaemia.

In study ITSA, LY900014 showed an accelerated insulin lispro absorption with a reduction in late insulin exposure compared to Humalog in children, adolescents, and adults with T1D. Furthermore, LY900014 reduced the late insulin lispro exposure compared to Humalog for all study populations, and the total insulin lispro exposure ($AUC_{[0\text{-}inf]}$) and t_{max} were comparable between LY900014 and Humalog in children, adolescents, and adults.

Additional data in paediatric patients with T2D are not required as per *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* (CPMP/EWP/1080/00 Rev. 1), since the clinical efficacy and safety of Lyumjev (LY900014) has been characterized in paediatric patients with T1D and in adults with T1D and T2D. Furthermore, faster absorption of LY900014 compared to Humalog was demonstrated after single dose via SC injection and via CSII in adult and paediatric patients with T1D. Consequently, if the B/R of Lyumjev is finally considered positive in paediatric patients with T1D, no paediatric efficacy and safety trial would be needed for approval of use of LY900014 in paediatric patients with T2D or in paediatric patients using CSII.

The B/R of Lyumjev in subjects aged 1 year and above is positive.

HRQoL Addendum

No differences between study groups were seen in quality of life as measured by the PedsQL questionnaire.

CGM addendum

Due to a failure to achieve the planned number of participants in the CGM Addendum substudy, the study was underpowered to show difference for the primary endpoint, the $iAUC_{0\text{-}2\ hours}$ comparison between LY900014 and Humalog. A numerical difference of 6.7 mg·h/dL in the postmeal $iAUC_{0–2\ hours}$ at Week 26 was observed, which was lower than expected by the MAH when planning the sample size (assumed mean difference of 22 mg·h/dL).

No nominal statistical differences were seen between study groups for time in target glucose ranges, time in hypoglycaemic glucose ranges or time spent in hyperglycaemic ranges. Numerically, postmeal administration of LY900014 was associated with less time in target level than premeal administration of LY900014 or Humalog especially during daytime (Figure 28).

Postprandial ambulatory glucose profiles, obtained in a small subset of subjects (n=28, 24, and 7, in the Humalog, LY900014 and LY900014+20 groups, respectively), were visually closely similar between all three study groups. However, postmeal administration of LY900014 seems to be associated with an increase at 1 hour after meals and a tendency toward hypoglycaemia at 4 hours (Figure 28). No differences were observed in within-day variability between treatments. Between-day variability, contrary to the MAH's claim, was numerically lesser in the Humalog group compared with the LY900014 group at Week 26. Overall, the differences between treatments in variability were overall relatively small or non-existent, depending on measure.

2.4.4. Conclusions on the clinical efficacy

LY900014 was non-inferior to Humalog in controlling glycaemia (HbA1c) whether administered prior to meal or after the meal. The results on postprandial glucose (PPG) excursions showing lower earlier postprandial glucose excursions with LY900014 vs. Humalog are not controlled for multiplicity.

The HbA1c results support the option to administer Lyumjev postprandially when necessary in children and adolescents, similarly to adults.

Few subjects below the age of 6 year old and none below the age of 3 year old were included in the ITSB trial. There is no concern that the efficacy would differ in children in this age group compared to older children.

From an efficacy point of view, the benefit-risk of LY900014 in subjects aged 1 year and above is positive.

2.5. Clinical safety

2.5.1. Introduction

The active substance of LY900014, insulin lispro, is known for more than 20 years. 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.

The most important adverse events of LY900014 observed in adults with T1D and T2D are hypoglycaemic events, as with all insulins. In the pivotal trials in adults, in both T1D and T2D patients, early post-meal hypoglycaemia was more frequent with LY900014 as compared with Humalog, whereas late post-meal hypoglycaemia was more frequent with Humalog. Overall incidence and rate of hypoglycaemic events was similar in adult T1D patients who were administered Humalog or LY900014 as MDI regimen. In T2D, the incidence and rate of documented hypoglycaemia was slightly higher with LY900014. No difference was seen between LY900014 and Humalog in the incidence of severe hypoglycaemia events in the pivotal trials

in adults.

A markedly higher incidence of injection and infusion site reactions (pain, itching, induration, erythema, and oedema) was observed in pivotal trials in adults in subjects administered LY900014 vs. Humalog. The incidence of these reactions was for MDI regimens 30 (2.7%) vs 1 (0.1%) ($p<0.0001$) for LY900014 and Humalog, respectively. In the studies on continuous subcutaneous insulin infusion (CSII) in adults, injection site reactions were also several-fold more common in subjects administered LY900014 than in subjects using Humalog. It is not certain if the increase in local reactions is due to direct irritation caused by the excipients of LY900014 or caused indirectly e.g., by increased blood vessel permeability (sodium citrate) and vasodilatation (treprostinil) at injection sites. However, no differences have been observed in adult studies for systemic hypersensitivity reactions between LY900014 and Humalog.
Please see Section 2.4.1.1.5 of this AR for description of safety assessments of study ITSB.

2.5.2. Patient exposure

A total of 418 patients received LY900014 in Study ITSB. Three-hundred and sixty-one (86%) of those patients were exposed to LY900014 for 180 days or more.

Table 37 summarizes exposure to study drug for Study ITSB.

Table 37. Summary of Exposure

Number of patients receiving study drug	716
Number of patients receiving LY900014	280
Number of patients receiving LY900014+20	138
Mean patient days of exposure to LY900014 (SD)	177.8 (30.0)
Mean patient days of exposure to LY900014+20 (SD)	182.1 (18.2)
Number of patients receiving Humalog	298
Mean patient days of exposure to Humalog (SD)	180.0 (23.4)

Abbreviation: SD = standard deviation.

2.5.3. Adverse events

The incidence of all TEAEs reported during the study was similar between the study intervention groups (Table 38).

Table 38 Summary of Adverse Events from Randomization to Safety Follow-up

	Humalog (N=298) n (%)	LY900014 (N=280) n (%)	LY900014+20 (N=138) n (%)
All TEAEs	144 (48.3)	131 (46.8)	52 (37.7)
Treatment-related TEAEs	9 (3.0)	28 (10.0)	6 (4.3)
Deaths	0	0	0
SAEs	12 (4.0)	6 (2.1)	2 (1.4)
AEs leading to discontinuation from study	0	2 (0.7)	0
AEs leading to discontinuation of treatment	0	2 (0.7)	0

Abbreviations: AE = adverse event; SAE = serious adverse event; N= number of subjects in analysis population; n= number of subjects with at least one adverse event per event type; TEAE = treatment-emergent adverse event.
Note: Relatedness determined by investigator. Patients can be counted in more than 1 category.

Overall, reporting of TEAEs was similar between treatment groups for each PT, except for injection site reactions and depression.

Thirty-four patients (4.7%) experienced at least 1 TEAE of injection site reactions, with a total of 46 events being reported. See section 2.5.6.1 of this AR for further details on injection site reactions.

There were 3 patients (2.2%) in the LY900014+20 treatment group who reported depression. Two events were moderate, 1 event was mild, and none were SAEs. No other events of depression were reported.

Nasopharyngitis and upper respiratory tract infection were the only TEAEs reported by at least 5% of patients. The incidence of patients reporting these TEAEs was similar among the 3 treatment groups.

2.5.4. Serious adverse event/deaths/other significant events

There were no treatment differences in the incidence of SAEs or in the incidence of SAEs for any PT.

A total of 20 patients (LY900014, 6 patients; LY900014+20, 2 patients; Humalog, 12 patients) reported >1 SAE during the study. Serious adverse events reported by more than 1 patient from randomization to follow-up were

1. Hypoglycaemia or hypoglycaemic coma, n=6 patients
    - Hypoglycaemia (n=5): Humalog, 2 patients (0.7%); LY900014, 3 patients (1.1%)
    - Hypoglycaemic coma (n=1): Humalog, 1 patient (0.3%)
2. Diabetic ketoacidosis (DKA), n=3 patients
    - LY900014, 2 patients (0.7%); LY900014 postmeal, 1 patient (0.7%)
        - One DKA event was considered related to study drug or procedure, as determined by the investigator. Upon further review, all 3 events were associated with disruption of prescribed dosing recommendations (missed basal insulin dose or insufficient bolus insulin dosing). All 3 events resolved following treatment with full recovery.

2.5.5. Hypoglycaemia

In Study ITSB, hypoglycaemia was assessed primarily using SMBG. Whenever hypoglycaemia was suspected, the patients were to 1) check their BG with a study-provided BG meter, and 2) record their BG value, the date and time, any associated symptoms, and the treatment administered in their study diary.

Hypoglycaemia was described using the following definitions:

- Documented Glucose Alert; BG≤3.9 mmol/L (70 mg/dL):
    - Documented symptomatic hypoglycaemia: an event with typical symptoms of hypoglycaemia.
    - Documented asymptomatic hypoglycaemia: an event without typical symptoms of hypoglycaemia.
    - Documented unspecified hypoglycaemia: with no information about symptoms of hypoglycaemia available (this has also been called unclassifiable hypoglycaemia).
- Documented Clinically Significant Hypoglycaemia with similar criteria as above, except for threshold BG<3.0 mmol/L (54 mg/dL)
    - Documented symptomatic hypoglycaemia
    - Documented asymptomatic hypoglycaemia
    - Documented unspecified hypoglycaemia
- Severe hypoglycaemia: during these episodes, patients have an altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and require assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG≤3.9 mmol/L (70 mg/dL)
    - Note: Young children will frequently require assistance with treatment of hypoglycaemia but are not experiencing signs of altered mental status or cognitive impairment. Final determination was made by the investigator and based on a severe hypoglycaemia event meeting the description provided above.
- Other hypoglycaemia:
    - Nocturnal hypoglycaemia: any documented hypoglycaemic event (including severe hypoglycaemia) that occurs between bedtime and waking.
    - Probable symptomatic hypoglycaemia: an event during which symptoms are present, but BG measurement was not reported.
    - Overall (or total) hypoglycaemia: this category combines all cases of hypoglycaemia (documented hypoglycaemia and probable symptomatic hypoglycaemia, including severe hypoglycaemia) excluding the events of relative hypoglycaemia. Nocturnal and severe hypoglycaemia are special cases of documented or probable hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, the event is only counted once in this category.

The final determination of a hypoglycaemic event as an episode of severe hypoglycaemia was made by the investigator based on the medical need of the child to have required assistance (that is, altered mental status or cognitive impairment) and was not predicated on the report of a child simply having received assistance. All episodes of severe hypoglycaemia were to be reported as SAEs.

Statistical analysis of hypoglycaemic events

The rate of severe hypoglycaemia per 100 years was compared between treatment groups using the empirical method that accounts for the heterogeneity between subjects in the underlying event rate. For each of the other categories of hypoglycaemia, the number of hypoglycaemia events during a specific period after randomization (for example, Weeks 0 to 12 of treatment period) were analysed using a negative binomial regression model. The model included treatment and age group as covariates. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days (or 30 days) was included in the model to standardise the rate of hypoglycaemia per year (or per 30 days). The proportion

of patients with at least 1 hypoglycaemic event in each category during a specific period after randomization was analysed using a logistic regression model including treatment and age group as covariates.

During assessment of the MAH's response to the first request for supplementary information (RSI), a discrepancy was noticed regarding results on hypoglycaemic events at baseline (i.e., during the lead-in period) reported in the interim clinical study report (CSR) and in the response to the first RSI. In the interim CSR submitted with the application, in children aged 3 to <6 years, a markedly higher mean baseline event rate of hypoglycaemia (calculated per year) was given for the Humalog group compared with the other two groups. The CSR reports a mean rate of documented hypoglycaemia <3.0 mmol/L (<54 mg/dL) of 112.8 in the Humalog group vs. 52.1 and 61.2, in the LY900014 and LY900014 postmeal groups, respectively. On the contrary, the model-based estimates given in table 5.1 of the response to the first RSI below indicated lower baseline event rate of hypoglycaemia in Humalog as compared with the LY900014 and LY900014+20 groups.

Response Table 5.1. Summary Statistics for Patient Characteristics by Age Groups

	Humalog	LY900014	LY900014+20	p-value[a]	p-value[b]
Age Group: 3-<6 year	**N = 7**	**N = 10**	**N = 10**		
Events of hypoglycaemia (<3.0 mmol/L) at baseline*, mean (SD)	1.0 (1.0)	4.0 (3.1)	4.7 (6.3)	0.025	0.150
Incidence of hypoglycaemia (<3.0 mmol/L) at baseline*, n (%)	4 (57.1)	8 (80.0)	8 (80.0)	0.364*[c]	0.364*[c]
Incidence of hypoglycaemia (<3.0 mmol/L) Week 0-26, n (%)	6 (85.7)	9 (90.0)	9 (90.0)	0.777*[c]	0.777*[c]
Week 26 HbA1c, mean (SD)	8.0 (0.7)	7.9 (1.2)	7.6 (0.6)	0.826	0.241
Change from baseline in HbA1c, LSMean (SE)	0.32 (0.36)	-0.45 (0.26)	-0.14 (0.25)	0.104*[d]	0.308*[d]
Age Group: 6-<12 year	**N = 98**	**N = 88**	**N = 40**		
Events of hypoglycaemia (<3.0 mmol/L) at baseline*, mean (SD)	1.8 (2.7)	1.6 (3.2)	1.6 (2.0)	0.657	0.622
Incidence of hypoglycaemia (<3.0 mmol/L) at baseline*, n (%)	53 (54.1)	46 (52.3)	21 (52.5)	0.807*[c]	0.864*[c]
Week 26 HbA1c, mean (SD)	7.7 (1.0)	7.9 (1.0)	8.0 (1.2)	0.384	0.201
Change from baseline in HbA1c, LSMean (SE)	0.04 (0.08)	0.08 (0.08)	0.29 (0.12)	0.660*[d]	0.075*[d]
Age Group: 12-<18 year	**N = 193**	**N = 182**	**N = 88**		
Events of hypoglycaemia (<3.0 mmol/L) at baseline*, mean (SD)	1.5 (2.2)	1.4 (2.4)	1.7 (2.8)	0.740	0.449
Incidence of hypoglycaemia (<3.0 mmol/L) at baseline*, n (%)	97 (50.3)	93 (51.1)	44 (50.0)	0.871*[c]	0.967*[c]
Week 26 HbA1c, mean (SD)	7.9 (1.2)	7.8 (1.2)	7.8 (1.0)	0.424	0.349
Change from baseline in HbA1c, LSMean (SE)	0.10 (0.07)	0.08 (0.07)	0.01 (0.10)	0.829*[d]	0.431*[d]

Abbreviations: HbA1c = haemoglobin A1c; LSMean = least squares mean; n = number of subjects with hypoglycemia; N = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error; vs = versus.

a LY900014 vs. Humalog.

b LY900014+20 vs. Humalog.

c p-value is from Logistic regression model for baseline comparisons between treatments: Incidence = Treatment.

d p-value is from ANCOVA model for HbA1c: Variable = Baseline HbA1c+ Pooled Country + Type of Basal Insulin at Randomisation + Treatment (Type III sum of squares).

* Baseline refers to the 4-week lead-in period when all patients were on Humalog.

Note: p-value is from t-test.

Note: N = 5 for Week 26 HbA1c and change from baseline in HbA1c for Humalog group age 3-<6 years. One patient (#01393) in Humalog group discontinued at Week 6 (Visit 7), and one patient #01781 had missing HbA1c value at Week 26.

The MAH clarified in their response to the second RSI that the programming instructions (Analysis Data Model [ADaM] specifications) were not followed to correct a permanent data issue that was identified prior to database lock. This programming error affected 9 patients in the full study population. For 7 patients, the baseline event rate was inflated because of the incorrect shortened duration (lead-in period start date was the same as the end date). For 1 patient in the 3 to less than 6 years of age cohort who received Humalog, the event rate for glucose less than 54 mg/dL (3.0 mmol/L) was incorrectly calculated as 730.5 events per year, but once corrected, it was reduced to 26.1 events per year. This patient had a significant impact on the Humalog group mean at baseline as reported in the CSR. According to the applicant, the

results given in the response to the first RSI were correct, as the programming error had been detected already when performing analyses for the response.

The model used in Lilly's response to the first RSI included the baseline number of events as a covariate, which is equivalent to using baseline hypoglycaemic rate when the baseline duration is approximately the same (4 weeks).

According to MAH, the 2 patients with post-baseline data errors were reported to have had very few hypoglycaemic events, and once the total duration was corrected, the rate was essentially the same. Thus, the MAH informed that this programming error had negligible impact on the overall results (p-values and LS means) and conclusions of the post-baseline event rates because the statistical model did not include baseline hypoglycaemic rate.

The updated subgroup analyses for glucose less than 54 mg/dL (3.0 mmol/L) for the full study population were submitted with the MAH's response to the second RSI. Remaining analyses on hypoglycaemic events and tables and figures thereof in the CSR were received upon request from the MAH with the response to third RSI. The text, tables and figures in this AR, which were compromised by the error, have been updated according to the final corrected analyses.

Severe hypoglycaemia

There were no treatment differences in the rate or incidence of severe hypoglycaemia. A total of 6 patients (LY900014, n=3; Humalog, n=3) experienced an episode of severe hypoglycaemia (table 39). Five of the six patients recovered after ingesting glucose in the form of food or drink and 1 patient recovered after having glucagon administered.

Table 39 Severe Hypoglycaemic Rate and Incidence from Randomization to Week 26

	Rate			Incidence		
Treatment	Mean (SD)	Aggregate Rate/100 Years	p-Value[a]	n (%)	Episodes	p-Value[b]
Lead-in Period (all patients treated with Humalog)						
Humalog (N=298)	3.95 (68.3)	4.38	0.956c	1 (0.3)	1	0.957[c]
LY900014 (N=280)	5.93 (99.2)	4.73	NC[d]	1 (0.4)	1	0.839[d]
LY900014+20 (N=138)	0	0	NC[e]	0	0	0.809[e]
Randomization to Week 26						
Humalog (N=298)	2.36 (24.3)	2.04	**0.**927[c]	3 (1.0)	3	0.929[c]
LY900014 (N=280)	2.07 (20.0)	2.20	NC[d]	3 (1.1)	3	0.414[d]

Treatment	Rate			Incidence		
	Mean (SD)	Aggregate Rate/100 Years	p-Value[a]	n (%)	Episodes	p-Value[b]
LY900014+20 (N=138)	0	0	NC[e]	0	0	0.389[e]

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

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

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

[c] LY900014 vs Humalog.

[d] LY900014+20 vs Humalog.

[e] LY900014+20 vs LY900014.

Note: The aggregated rate was calculated using the total number of severe hypoglycaemic episodes divided by the cumulative days on treatment from all patients within a treatment group, times 365.25 (for rate per 100 years).

Incidence of all documented, nocturnal, and non-nocturnal hypoglycaemia

Rates of hypoglycaemia from randomisation to week 26 are given in tables 5.5.5.2 [for BG <3.0 mmol/L (<54 mg/dL)] and 5.5.5.3 [for BG <3.9 mmol/L (≤70 mg/dL)].

There were no treatment differences in the rate of all documented hypoglycaemia with BG <3.0 mmol/L (<54 mg/dL). Also, the incidence was similar between the 3 treatment groups with this glycaemic threshold.

Table 40 Hypoglycaemia Rate (Adjusted for 1 Year) from Randomisation to Week 26 for BG <3.0 mmol/L (<54 mg/dL)

Category/Subcategory of Hypoglycaemia	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 <54 mg/dL, (3.0 mmol/L)		
Documented hypoglycaemia		
Humalog (N=298)	16.6 (1.23)	A: 0.97 (0.78, 1.19), p=0.737
LY900014 (N=280)	16.1 (1.20)	B: 1.07 (0.82, 1.39), p=0.635
LY900014+20 (N=138)	17.7 (1.99)	C: 1.10 (0.85, 1.44), p=0.462
Nocturnal hypoglycaemia		
Humalog (N=298)	1.1 (0.19)	A: 0.65 (0.40, 1.07), p=0.093
LY900014 (N=280)	0.7 (0.13)	B: 0.62 (0.32, 1.18), p=0.142
LY900014+20 (N=138)	0.7 (0.19)	C: 0.95 (0.49, 1.82), p=0.866
Non-nocturnal hypoglycaemia		
Humalog (N=298)	12.8 (1.04)	A: 0.99 (0.80, 1.24), p=0.946
LY900014 (N=280)	12.7 (1.00)	B: 1.03 (0.78, 1.37), p=0.839
LY900014+20 (N=138)	13.2 (1.58)	C: 1.04 (0.78, 1.37), p=0.796

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

There were no significant differences in the rate of all documented, nocturnal or non-nocturnal hypoglycaemia with BG <3.9 mmol/L (≤70 mg/dL) between LY900014, Humalog and LY900014+20 (table 41). However, the incidence of all documented hypoglycaemia with BG <3.9 mmol/L (≤70 mg/dL) was lower for LY900014+20 compared to Humalog (LY900014+20, n=121 [87.7%]; Humalog, n=280 [94.0%]); non-nocturnal hypoglycaemia for LY900014+20 versus Humalog (n=116 [84.1] versus

n=270 [90.6%], p=0.044), and nocturnal hypoglycaemia for LY900014+20 versus LY900014 (n=46 [33.3%] versus n=129 [46.1%], p=0.015).

There were no other significant differences for the incidence of all documented, nocturnal, and non-nocturnal hypoglycaemia between treatment groups at baseline or Weeks 0 to 26.

Table 41 Hypoglycaemia Rate (Adjusted for 1 Year) from Randomisation to Week 26 for BG <3.9 mmol/L (≤70 mg/dL)

Category/Subcategory of Hypoglycaemia	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 hypoglycaemia		
Humalog (N=298)	78.0 (4.23)	A: 0.96 (0.82, 1.13), p=0.635
LY900014 (N=280)	75.1 (4.44)	B: 0.98 (0.81, 1.18), p=0.803
LY900014+20 (N=138)	76.1 (6.10)	C: 1.01 (0.83, 1.23), p=0.889
Nocturnal hypoglycaemia		
Humalog (N=298)	3.9 (0.50)	A: 0.89 (0.63, 1.24), p=0.474
LY900014 (N=280)	3.5 (0.39)	B: 0.77 (0.47, 1.27), p=0.312
LY900014+20 (N=138)	3.0 (0.66)	C: 0.87 (0.54, 1.42), p=0.586
Non-nocturnal hypoglycaemia		
Humalog (N=298)	55.1 (3.42)	A: 1.01 (0.84, 1.20), p=0.931
LY900014 (N=280)	55.5 (3.63)	B: 0.96 (0.78, 1.18), p=0.690
LY900014+20 (N=138)	52.8 (4.62)	C: 0.95 (0.77, 1.18), p=0.643

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

Rate and Incidence of Post-dose Hypoglycaemia

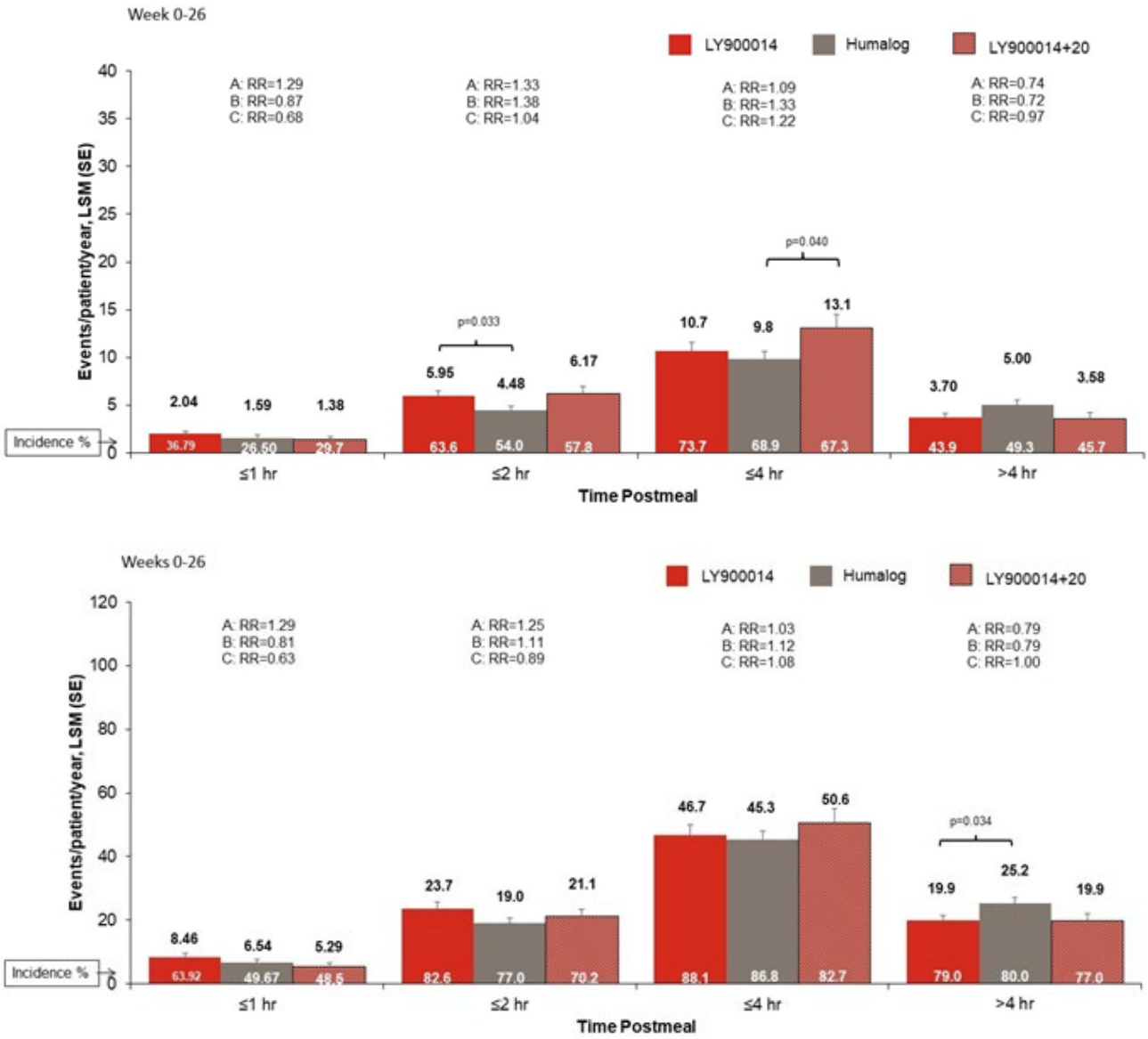
Results on hypoglycaemia analysed relative to the time of the most recent mealtime dose given ("post-dose") are presented in Figure 28.

For the time from Week 0 to Week 26, for BG <3.0 mmol/L (<54 mg/dL), there was a higher rate of documented hypoglycaemia for

- LY900014 versus Humalog at ≤2 hours post-dose (RR [95% CI] = 1.33 [1.02, 1.72])
- LY900014+20 versus LY900014 at >2 to ≤4 hours post-dose (RR [95% CI] = 1.45 [1.05, 2.01]), and
- for LY900014+20 versus Humalog at ≤4 hours post-dose (RR [95% CI] = 1.33 [1.01, 1.74]).

For BG ≤3.9 mmol/L (≤70 mg/dL), there was a lower rate of documented hypoglycaemia for LY900014 versus Humalog at >4 hours after the start of the prandial dose (RR [95% CI] = 0.79 [0.64, 0.98]).

Figure 28 Rate and incidence of documented post-dose hypoglycaemia BG <3.0 mmol/L (<54 mg/dL) (top panel) and for BG ≤3.9 mmol/L (≤70 mg/dL) (bottom panel) from Weeks 0 to 26.



Subgroup Analyses for Hypoglycaemia

For all the documented hypoglycaemia based on the threshold of BG ≤3.9 mmol/L (70 mg/dL) and <3.0 mmol/L (54 mg/dL), event rate was analysed using a negative binomial model, which includes treatment, subgroup and 2-way interaction of subgroup, and treatment.

The rate and incidence of all documented hypoglycaemia were analysed by the following subgroups in study ITSB: age group (Age Group 1, Age Group 2); HbA1c stratum; region; type of basal insulin; prandial insulin dosing plan; personal CGM/FGM use, and TEADA status.

For hypoglycaemia with the threshold of BG <3.0 mmol/L (54 mg/dL), the only observed treatment-by-subgroup interaction was the "Age Group 2" analysis. Age Group 2 categorized patients into 3 age cohorts: 0 to <6, 6 to <12, and 12 to <18 years of age. Of note, no subjects <3 years of age participated in the study. In Age Group 2, the relative rate of hypoglycaemia with BG <3.0 mmol/L (54 mg/dL) for Weeks

0 to 26 was higher for LY900014 and LY900014+20 compared to Humalog, which was driven by the 3 to <6 age cohort, in which the relative rate of hypoglycaemia was around 3–4 times higher in the LY900014 and LY900014+20 groups than in the Humalog group (table 42). This treatment-by-subgroup interaction is interpreted by the MAH to be spurious due to the small number of patients in the 0 to <6 age cohort who reported the majority of the hypoglycaemic events. Out of the 20 patients in Age Group 3 to <6 years exposed to LY900014 (10 with preprandial and 10 with postprandial administration), 18 experienced at least 1 hypoglycaemic event (BG <3.0 mmol/L [54 mg/dL]) during the treatment period. Of the 18 patients who experienced at least 1 hypoglycaemic event, one third of patients experienced between 20 and 66 hypoglycaemic events. Out of the 18 patients who experienced at least 1 hypoglycaemic event during the treatment period, 16 patients came from 2 sites in Brazil (n=8) and 2 sites in Ukraine (n=8). One 3-year-old subject experienced a severe hypoglycaemic event with prolonged recovery after food/drink.

Table 42 moreover shows that in the Humalog groups, the LS Mean rate of hypoglycaemia <3.0 mmol/L (54 mg/dL) from randomisation to Week 26 was about half of the rate seen in older children and adolescents. On the contrary, in the LY900014 and LY900014+20 groups, the event rate in children aged 3 to <6 years was about double the rate seen in older children and adolescents. In the age groups of children from 6 to <12 years and adolescents aged 12 to <18 years, the rate of hypoglycaemic events/patient/year were in the same range in all age groups. Hence, the marked difference noted in the youngest age group was partly due to both a greater numerical rate of events in the LY900014 and LY900014+20 groups and a lower numerical rate of events in the Humalog group when compared with older children and adolescents.

Table 42 Event Rate for All Documented Hypoglycaemia <3.0 mmol/L (54 mg/dL) (Events/Patient/Year) from baseline to Week 26

a) subjects aged 3 to <6 years

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

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

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

b) subjects aged 6 to <12 years

Variable Analyzed: All Documented Hypoglycemia with Glucose < 54 mg/dL when Pooled Age Group 2 = 6-<12

Time Point Treatment	N	Mean (SD)	(Min, Med, Max)	LSMean (SE) *a*b
0<wk<=26				
Humalog	98	19.0 (25.36)	(0.0,10.1, 133.7)	19.0 (2.56)
LY900014	88	16.1 (19.20)	(0.0, 9.8, 99.8)	16.2 (2.04)
LY900014 Postmeal	40	15.2 (17.80)	(0.0,12.1, 80.8)	15.3 (2.79)

Pairwise Comparison (A vs B)	Relative Rate (Treatment A/B) (95% CI)*a*b	p-value*a*b
LY900014 vs Humalog	0.85 (0.59,1.22)	0.376
LY900014 Postmeal vs Humalog	0.81 (0.52,1.26)	0.341
LY900014 Postmeal vs LY900014	0.95 (0.61,1.47)	0.812

c) subjects aged 12 to <18 years

Variable Analyzed: All Documented Hypoglycemia with Glucose < 54 mg/dL when Pooled Age Group 2 = 12-<18

Time Point Treatment	N	Mean (SD)	(Min, Med, Max)	LSMean (SE) *a*b
0<wk<=26				
Humalog	193	15.8 (19.59)	(0.0, 9.8,135.7)	15.8 (1.41)
LY900014	182	15.1 (19.81)	(0.0, 9.7,146.9)	15.3 (1.48)
LY900014 Postmeal	88	16.7 (22.90)	(0.0, 7.1,102.6)	16.7 (2.43)

Pairwise Comparison (A vs B)	Relative Rate (Treatment A/B) (95% CI)*a*b	p-value*a*b
LY900014 vs Humalog	0.97 (0.75,1.25)	0.807
LY900014 Postmeal vs Humalog	1.06 (0.76,1.48)	0.733
LY900014 Postmeal vs LY900014	1.09 (0.78,1.54)	0.605

Abbreviations: CI = confidence interval; Max = maximum; Med = median; Min = minimum; N = number of subjects in the population with baseline and post-baseline value at the specified time point; SD = standard deviation; SE = standard error.

Note 1: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.

*a - Negative binomial model for baseline comparisons between treatment and control groups: Number of episodes = Treatment, with log (exposure in days/365.25) as an offset variable.
*b - Negative binomial model for post-baseline comparisons between treatment and control groups: Number of episodes = Pooled Age Group 1 + Treatment, with log (exposure in days/365.25) as an offset variable.
*c - Full model for subgroup by treatment interaction at baseline: Number of episodes = Treatment + Pooled Age Group 2 + Treatment*Pooled Age Group 2.
*d - Full model for subgroup by treatment interaction: Number of episodes = Pooled Age Group 1 + Treatment + Pooled Age Group 2 + Treatment*Pooled Age Group 2.

For hypoglycaemia with BG ≤3.9 mmol/L (70 mg/dL), there was a treatment-by-subgroup interaction for personal CGM/FGM use. The rate of hypoglycaemia was similar for LY900014 and Humalog if patients used a personal CGM/FGM during the treatment period from baseline to Week 26 (relative rate = 1.05). The rate of hypoglycaemia was lower for LY900014 compared to Humalog if patients were not using a personal CGM/FGM (relative rate = 0.80).

A major objection was raised due to the increased hypoglycaemia risk in children <6 years of age for hypoglycaemic events <3.0 mmol/L (54 mg/dL). In their response to the first RSI, the MAH submitted summary statistics by age groups. The MAH explains the difference to be partly due to differences in baseline hypoglycaemia risk in the three treatment groups, defined as hypoglycaemic events occurring during the lead-in period when all patients were treated with Humalog. It is agreed that there was an imbalance in the rate of hypoglycaemia in this age group in favour of Humalog compared with the other treatment groups at baseline in the analyses submitted with the response. During the 4 weeks of the lead-in period, the mean (SD) events of hypoglycaemia <3.0 mmol/L (54 mg/dL) was for Humalog 1.0 (1.0), for LY900014 4.0 (3.1), and for LY900014+20: 4.7 (6.3). However, even when adjusting for baseline hypoglycaemia and achieved HbA1c at week 26, there remained a more than 2-fold risk for hypoglycaemia in the LY900014 and LY900014+20 groups vs. Humalog, even if the difference was no more statistically significant after the adjustments. Moreover, the further analyses on the rate of hypoglycaemia in the age group <6 years submitted by the MAH in the response to the first RSI identified two children with a very high rate of hypoglycaemic events <3.0 mmol/L (54 mg/dL), one in the LY900014 group and one in the LY900014+20 group both of whom had high hypoglycaemia rate already at baseline. The remaining difference in hypoglycaemia risk after adjusting the hypoglycaemia rate for baseline rate and achieved HbA1c level is driven by these outliers.

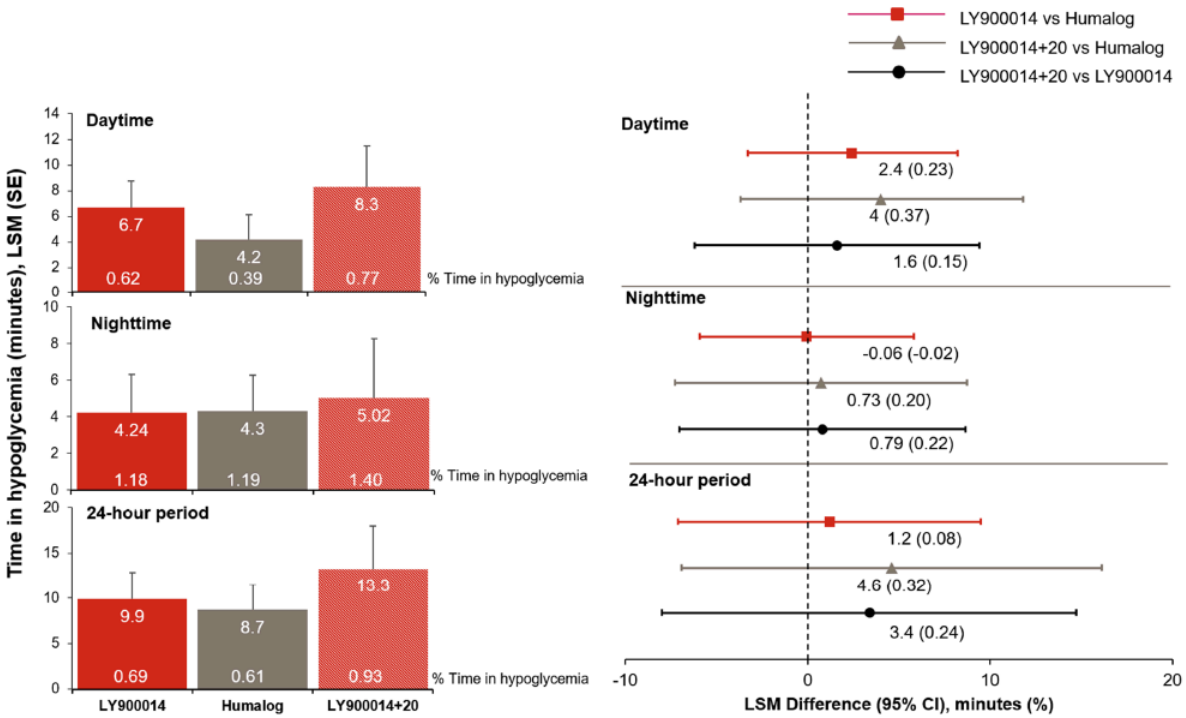
The MAH did not consider addition of any warnings regarding hypoglycaemia risk in this age group to be warranted, and no warning is required based on analyses included in the MAH's response to the first RSI.

Time in Hypoglycaemic and Hyperglycaemic BG ranges/CGM Addendum

In the CGM Addendum of ITSB, time spent in hypoglycaemia and in hyperglycaemia were assessed as secondary endpoints. Note: due to insufficient enrolment in the CGM Addendum, and the subsequent lack of study power, it is not possible to draw definitive interpretations of the data collected in this addendum (see Section 2.4.1.3 of this AR).

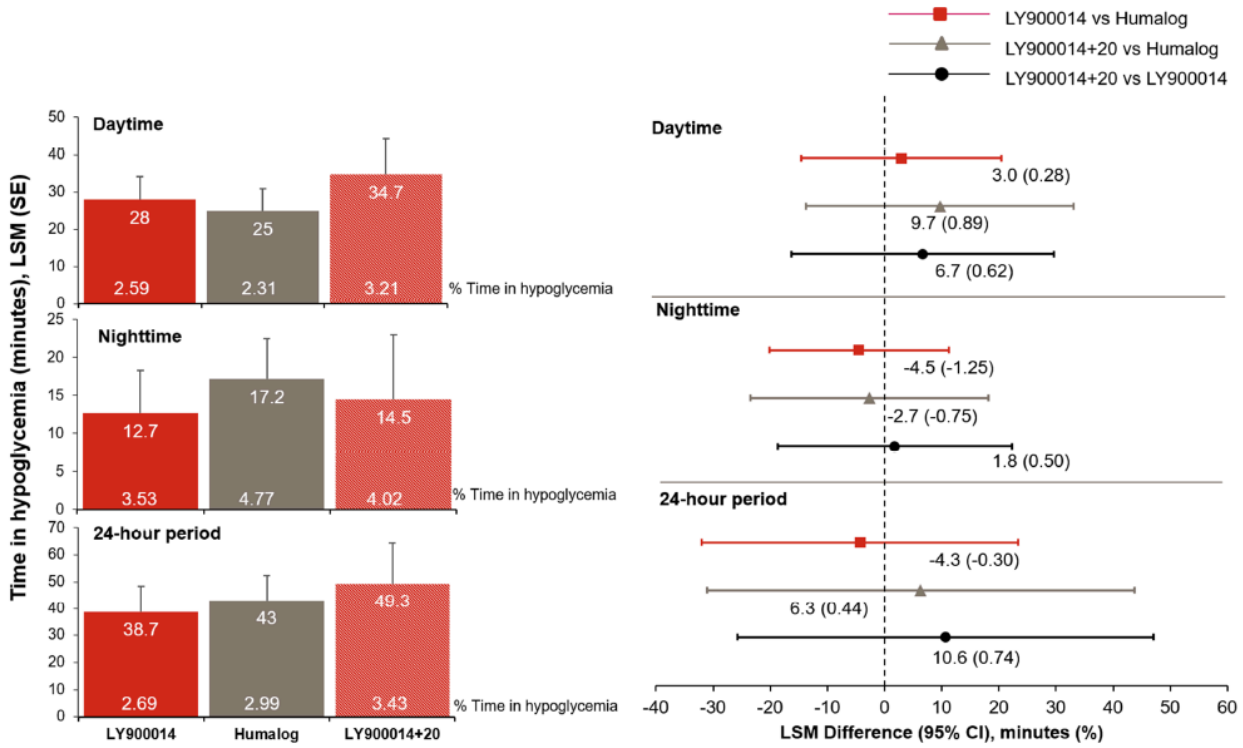
Figures 5.5.5.2 and 5.5.5.3 illustrate the time spent in hypoglycaemia at Week 26 at the blood glucose thresholds of <3.0 mmol/L (54 mg/dL) and BG ≤3.9 mmol/L (70 mg/dL), respectively. None of the noted differences were statistically significant.

Figure 29 Time in hypoglycaemic range [<3.0 mmol/L (54 mg/dL)] for 24-hour period at Week 26



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

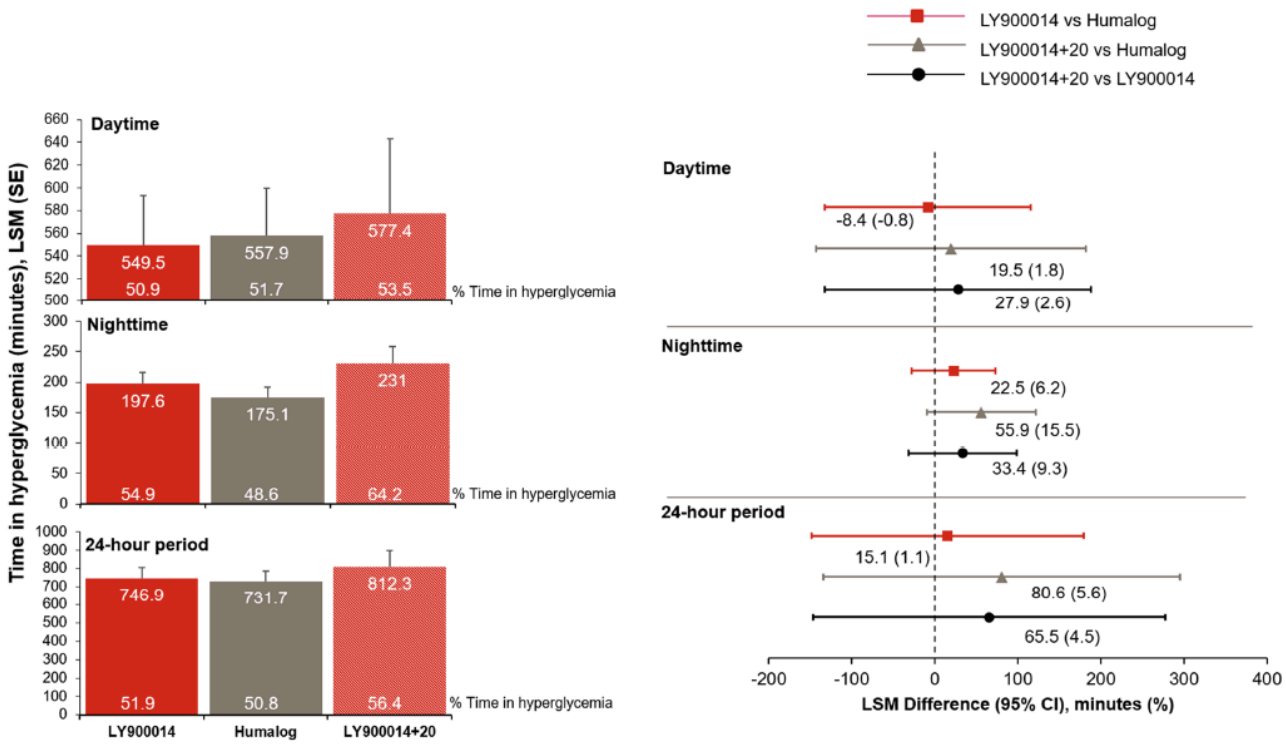
Figure 30 Time in hypoglycaemic range [BG ≤3.9 mmol/L (70 mg/dL)], for 24-hour period at Week 26



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

Time in Hyperglycaemic Glucose Ranges was also assessed as an exploratory endpoint of the CGM Addendum. Analyses were performed for time spent in hyperglycaemia (>10.0 mmol/L [180 mg/dL], >13.9 mmol/L [250 mg/dL], and 10.1 to 13.9 mmol/L [181 to 250 mg/dL]) for daytime, night-time, and over a 24-hour period at baseline and Week 26. No statistically significant differences were noted for any threshold or any period of time. Figure 31 illustrates results for the time in the range >10.0 mmol/L (180 mg/dL), at Week 26.

Figure 31 Time in hyperglycaemic range (>10.0 mmol/L [180 mg/dL]), at Week 26



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

2.5.6. Hypersensitivity

2.5.6.1. Injection site reactions

A customized MedDRA search of spontaneously reported AEs was used to identify potential injection site reactions. An eCRF was also used to collect information on the presence and severity of injection site erythema, induration, pain, pruritus, and oedema for injection site reactions during the study.

A total of 34 patients (4.7%) experienced at least 1 TEAE of injection site reaction, with a total of 46 events being reported. All of the injection site reactions were mild or moderate in severity.

More patients in the LY900014 treatment group had injection site reactions compared to Humalog:

- Humalog: n=8 (2.7%)
- LY900014: n=22 (7.9%), and
- LY900014+20: n=4 (2.9%).

Most events experienced by patients in the LY900014 groups were reported as

- injection site reaction (LY900014, n=11; LY900014+20, n=2)
- injection site erythema (LY900014=4; LY900014+20=0), and
- injection site pain (LY900014, n=4; LY900014+20, n=1).

Two patients in the LY900014 treatment group discontinued study treatment due to AEs of injection site reactions.

2.5.6.2. Systemic Hypersensitivity Reaction

Three SMQs were used to identify potential systemic hypersensitivity reactions from the spontaneously reported AEs, namely, Anaphylactic reaction (SMQ), Angioedema (SMQ), and Hypersensitivity (SMQ).

There were 36 patients (5.0%) who experienced ≥1 TEAE by broad search terms and 22 patients (3.1%) who experienced ≥1 TEAE of hypersensitivity by narrow search terms. None of these hypersensitivity reactions were serious. There were no discontinuations of the study or study drug due to hypersensitivity reactions.

Rhinitis (0.7%), dermatitis (0.2%), rash (0.5%), and hypersensitivity (0.5%) were the most common events reported with LY900014 treatment. There were more patients in the LY900014+20 group (n=4, 2.9%) versus the Humalog group (n=2, 0.7%) and LY900014 group (n=1, 0.4%) who experienced events included among broad search terms for angioedema (Table 43).

Table 43 Potential Treatment-Emergent Systemic Hypersensitivity Reactions Using MedDRA Search Terms From Randomization to Safety Follow-up, Safety Population

SMQ or sub-SMQ Classification Preferred Term	Humalog (N=298) n (%)	LY900014 (N=280) n (%)	LY900014 Postmeal (N=138) n (%)	Total (N=716) n (%)
Subjects with >= 1 - TEAE				
Broad	14 (4.7)	14 (5.0)	8 (5.8)	36 (5.0)
Narrow	11 (3.7)	6 (2.1)	5 (3.6)	22 (3.1)
Hypersensitivity (SMQ)				
Broad	11 (3.7)	10 (3.6)	6 (4.3)	27 (3.8)
Rhinitis allergic	2 (0.7)	2 (0.7)	1 (0.7)	5 (0.7)
Dermatitis allergic	3 (1.0)	1 (0.4)	0	4 (0.6)
Rash	2 (0.7)	1 (0.4)	1 (0.7)	4 (0.6)
Hypersensitivity	1 (0.3)	0	2 (1.4)	3 (0.4)
Conjunctivitis	1 (0.3)	1 (0.4)	0	2 (0.3)
Dermatitis	0	2 (0.7)	0	2 (0.3)
Erythema	0	2 (0.7)	0	2 (0.3)
Allergy test positive	1 (0.3)	0	0	1 (0.1)
Anaphylactic reaction	1 (0.3)	0	0	1 (0.1)
Asthma	1 (0.3)	0	0	1 (0.1)
Asthmatic crisis	0	1 (0.4)	0	1 (0.1)
Bronchial hyperreactivity	0	0	1 (0.7)	1 (0.1)
Eczema	0	1 (0.4)	0	1 (0.1)
Gingival swelling	0	0	1 (0.7)	1 (0.1)
Idiopathic urticaria	0	0	1 (0.7)	1 (0.1)
Lip swelling	1 (0.3)	0	0	1 (0.1)
Pruritus	0	0	1 (0.7)	1 (0.1)
Urticaria	1 (0.3)	0	0	1 (0.1)
Narrow	11 (3.7)	6 (2.1)	5 (3.6)	22 (3.1)
Rhinitis allergic	2 (0.7)	2 (0.7)	1 (0.7)	5 (0.7)
Dermatitis allergic	3 (1.0)	1 (0.4)	0	4 (0.6)
Rash	2 (0.7)	1 (0.4)	1 (0.7)	4 (0.6)
Hypersensitivity	1 (0.3)	0	2 (1.4)	3 (0.4)
Dermatitis	0	2 (0.7)	0	2 (0.3)
Allergy test positive	1 (0.3)	0	0	1 (0.1)
Anaphylactic reaction	1 (0.3)	0	0	1 (0.1)
Eczema	0	1 (0.4)	0	1 (0.1)
Gingival swelling	0	0	1 (0.7)	1 (0.1)
Idiopathic urticaria	0	0	1 (0.7)	1 (0.1)
Lip swelling	1 (0.3)	0	0	1 (0.1)
Urticaria	1 (0.3)	0	0	1 (0.1)
Anaphylactic reaction (SMQ)				
Broad	8 (2.7)	6 (2.1)	4 (2.9)	18 (2.5)
Cough	2 (0.7)	3 (1.1)	2 (1.4)	7 (1.0)
Rash	2 (0.7)	1 (0.4)	1 (0.7)	4 (0.6)
Erythema	0	2 (0.7)	0	2 (0.3)
Anaphylactic reaction	1 (0.3)	0	0	1 (0.1)
Asthma	1 (0.3)	0	0	1 (0.1)
Dyspnoea	0	1 (0.4)	0	1 (0.1)
Hypotension	1 (0.3)	0	0	1 (0.1)
Lip swelling	1 (0.3)	0	0	1 (0.1)
Pruritus	0	0	1 (0.7)	1 (0.1)
Urticaria	1 (0.3)	0	0	1 (0.1)
Narrow	1 (0.3)	0	0	1 (0.1)
Anaphylactic reaction	1 (0.3)	0	0	1 (0.1)
Angioedema (SMQ)				
Broad	2 (0.7)	1 (0.4)	4 (2.9)	7 (1.0)
Hypersensitivity	1 (0.3)	0	2 (1.4)	3 (0.4)
Peripheral swelling	1 (0.3)	1 (0.4)	0	2 (0.3)
Gingival swelling	0	0	1 (0.7)	1 (0.1)
Idiopathic urticaria	0	0	1 (0.7)	1 (0.1)
Lip swelling	1 (0.3)	0	0	1 (0.1)
Urticaria	1 (0.3)	0	0	1 (0.1)
Narrow	1 (0.3)	0	2 (1.4)	3 (0.4)
Gingival swelling	0	0	1 (0.7)	1 (0.1)
Idiopathic urticaria	0	0	1 (0.7)	1 (0.1)
Lip swelling	1 (0.3)	0	0	1 (0.1)
Urticaria	1 (0.3)	0	0	1 (0.1)

Abbreviations: LY900014 Postmeal = LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal; N = number of subjects in the analysis population; n = number of subjects in the specified category.

2.5.7. Treatment-emergent anti-drug antibodies

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

There were no meaningful differences in incidence of treatment-emergent anti-insulin lispro antibodies (TEADA) between the treatment groups (Humalog, LY900014, LY900014 + 20) post baseline (table 44). Similarly, there were no meaningful differences between the treatment groups in cross-reactivity to native insulin.

Table 44 Summary of Postbaseline ADA

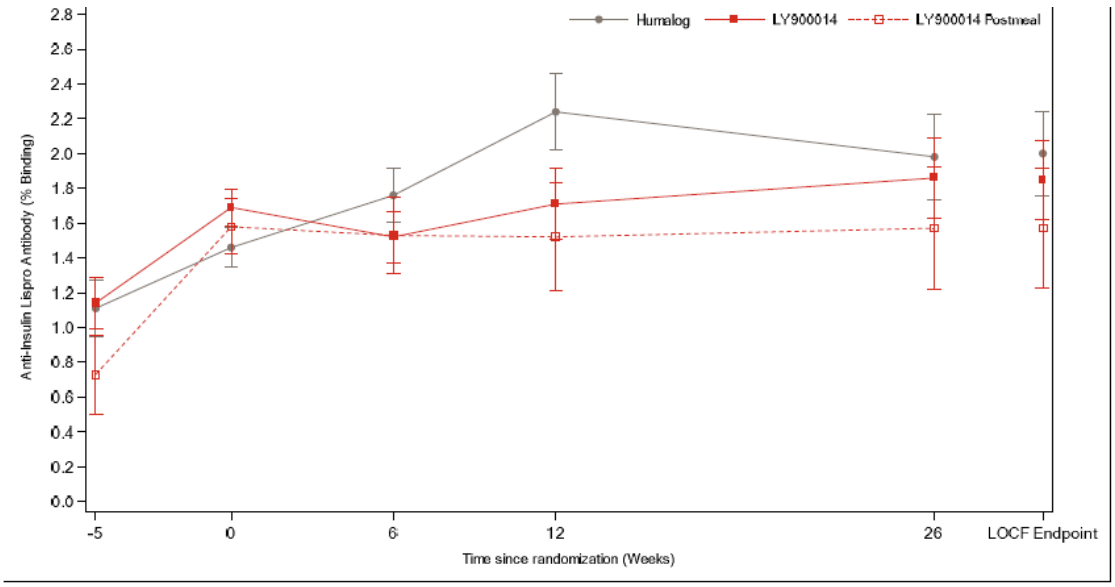
Category	Humalog	LY900014	LY900014+20
TEADA evaluable, n	287	268	131
TEADA positive, n (%)	75 (26.1)	85 (31.7)	37 (28.2)
Treatment-induced ADA positive, n (%)[a]	27 (9.4)	31 (11.6)	20 (15.3)
Treatment-boosted ADA positive, n (%)[a]	48 (16.7)	54 (20.1)	17 (13.0)
Cross-reactive ADA to LY900014, n (%)[a]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

Abbreviations: ADA = anti-drug antibody; n= number of subjects; TEADA = treatment-emergent ADA.

[a] Denominator = TEADA positive n value.

No differences between treatment groups were observed in percent binding of anti-insulin antibodies during the study (Figure 32)

Figure 32 Plot of anti-insulin lispro antibody percent binding. Visit-wise raw mean from randomization to Week 26. Safety population with positive TEADA response excluding China.



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

In subgroups analyses, TEADA status was not related to HbA1c or hypoglycaemia. The development of TEADA was not associated with an increased risk for hypersensitivity or injection site reactions. (Data not shown for brevity)

2.5.8. Laboratory findings and Vital Signs

There were no clinically meaningful treatment differences in chemistry laboratory tests at the last observation carried forward endpoint, haematology laboratory values, or in the incidence of treatment emergent abnormal laboratory values (data not shown for brevity).

The were no clinically meaningful differences in the vital sign measurements, physical examination assessments, or other observations related to safety in Study ITSB. There were no treatment differences in the proportions of patients with treatment-emergent high or low vital signs (data not shown for brevity).

Discontinuation due to adverse events

Two patients (0.3%), both from the LY900014 treatment group, reported AEs leading to treatment discontinuation: one reported moderate injection site pain and the other reported mild injection site reaction.

Post marketing experience

The safety and efficacy of insulin lispro are well established through the Humalog development program and over 20 years of postmarketing experience. No postmarketing experience is available for LY900024, since it has so far been indicated for use in adults only.

2.5.9. Discussion on clinical safety

The collection of safety data was appropriately planned in study ITSB. The definitions used for describing hypoglycaemia were in line with international recommendations for diabetes trials. Immunogenicity testing was performed adequately. Safety monitoring was conducted in compliance with international regulations and GCP guidelines.

There were no deaths. There were no marked differences in the incidence of SAEs between treatments. The SAEs reported by more than 1 patient were hypoglycaemia or hypoglycaemic coma (6 subjects), including 5 reported as hypoglycaemias, of which 2 (0.7%) in the Humalog group and 3 (1.1%), in the LY900014 group; 1 hypoglycaemic coma (in the Humalog group), and 3 cases of diabetic ketoacidosis (DKA). The DKA cases occurred in 2 patients (0.7%) in the LY900014 group and 1 patient (0.7%) in the LY900014+20. In all cases of DKA, the reason was determined to be due to non-compliance of the prescribed guidelines or omission of necessary insulin administration.

The overall rate and incidence of hypoglycaemia observed in paediatric patients in Study ITSB with LY900014 treatment is consistent with the hypoglycaemia findings in adult patients with diabetes who were treated with LY900014. The incidence for documented, nocturnal, and non-nocturnal hypoglycaemia was similar between LY900014 and Humalog for the BG threshold <3.0 mmol/L (54 mg/dL). For the higher BG threshold (BG ≤3.9 mmol/L [70 mg/dL]), the incidence of documented and non-nocturnal hypoglycaemia was lower in the LY900014+20 group (postprandial administration) vs. Humalog, and the incidence of nocturnal hypoglycaemia was lower in the LY900014+20 group vs. LY900014 group. However, no difference was seen in the incidence of hypoglycaemic events between pre-prandially administered Lyumjev and Humalog. Furthermore, there were no significant differences between treatment groups for the rates/year of all documented, nocturnal, and non-nocturnal hypoglycaemia at baseline and from Weeks 0 to 26 when using either the threshold of BG threshold <3.0 mmol/L (54 mg/dL) or BG ≤3.9 mmol/L (70 mg/dL). More information was requested to understand why the total incidence and rate of hypoglycaemic events seemed to be larger than the sum of nocturnal and non-nocturnal hypoglycaemic events for all three treatment groups (see Tables 5.5.5.2 and 5.5.5.3). The MAH clarified this issue in their response to the first RSI: the total incidence and rate of hypoglycaemic events included all documented symptomatic, documented asymptomatic, unclassifiable and severe events, whereas the table on nocturnal and non-nocturnal hypoglycaemia included documented symptomatic and severe events.

In subjects aged 3 to <6 years, the rate of hypoglycaemia below BG <3.0 mmol/L (54 mg/dL) was 3−4-fold higher in the LY900014 and LY900014+20 group than in the Humalog group. Compared with older children and adolescents, the 3- to <6-year-old subjects had a lower rate of hypoglycaemia in the Humalog group but a higher rate of hypoglycaemia in the LY900014 and LY900014+20 groups. Out of the 20 patients exposed to LY900014 (10 with preprandial and 10 with postprandial administration) in Age Group 3 to <6 years, 18 experienced at least 1 hypoglycaemic event (BG <3.0 mmol/L [54 mg/dL]) during the treatment

period. Out of the 18 patients who experienced at least 1 hypoglycaemic event during the treatment period, 16 patients came from 2 sites in Brazil (n=8) and 2 sites in Ukraine (n=8). One 3-year-old subject experienced a severe hypoglycaemic event with prolonged recovery after food/drink. According to the MAH, regional differences in the management of T1D in children may have impacted insulin dose titration in this younger age group and may have contributed to increased hypoglycaemia observed at these sites. On the other hand, since there were only 27 subjects aged 3 to <6 years in this subgroup analysis (n=7, 10, and 10 in the Humalog, LY900014 and LY900014+20 groups, respectively), the 16 subjects from Brazil and Ukraine with hypoglycaemia <3.0 mmol/L (54 mg/dL) constituted a majority of all subjects in this age group. Due to the low number of subjects in this age group, firm conclusions on risk of hypoglycaemia in these youngest patients cannot be drawn. It is noteworthy that the overall glycaemic control was similar across age groups and does not explain the excess risk of hypoglycaemia in the youngest age group. More detailed information on this issue was requested for assessment of safety of LY900014 in youngest children.

It is also noteworthy that even though inclusion criteria would have allowed subjects from age of 1 year, none below 3 years of age were included in the study. The MAH was requested to submit a detailed analysis of hypoglycaemic events in patients aged 3 to 12 years vs. other paediatric age groups and to discuss if the excess risk of hypoglycaemia in the youngest age group should be reflected in the Product Information.

Further analyses provided by the MAH showed that the timing of the hypoglycaemia events in relation to the meal were relatively similar between treatment groups in children aged 3 to <12 years. The majority of events occurred after the first hour with most events seen at 2 to less than 4 hours (Humalog 31.6%; LY900014 33.2%; LY900014 postmeal 37.6%). The majority of hypoglycaemia events in children aged 3 to <12 years occurred during the non-nocturnal time in all 3 treatment groups (Humalog 88.1%; LY900014 89.4%; LY900014 postmeal 89.8%). Data on timing of hypoglycaemia were not given separately for children aged 3 to <6 years. Analysis of HbA1c at Week 26 versus post-baseline hypoglycaemia event rate for all patients aged 3–<12 years showed increase in hypoglycaemia with HbA1c <8.0 % in all treatment arms, which is expectable. An analysis on the relation of insulin dosage and hypoglycaemic events demonstrated less hypoglycaemia with larger insulin dose, which reflects easier control of hypoglycaemia in older children, who are bigger and therefore have a higher total insulin dose.

In their response to the first RSI, the MAH submitted summary statistics for patient characteristics by age groups. At baseline, children aged 3–<6 years who were randomised to either the LY900014 or LY900014+20 treatment group had more hypoglycaemic events <3.0 mmol/L (54 mg/dL) compared to Humalog (Humalog: 1.0, LY900014: 4.0 and LY900014+20: 4.7 events). After adjusting for both baseline hypoglycaemia and for HbA1c at Week 26, the differences were no longer statistically significant, but the numerical difference in the rate of hypoglycaemia <3.0 mmol/L (54 mg/dL) remained more than 2-fold in the LY900014 and LY900014+20 groups compared with the Humalog group. Baseline hypoglycaemic events were events that occurred during the lead-in period when all patients were treated with Humalog. Such imbalance at baseline occurs easily by chance when the number of subjects is low and may indeed have major impact on results. Hence, lower baseline hypoglycaemia in the Humalog group vs. the other two groups could partly explain the observed difference in hypoglycaemia rate between the Humalog group and the two LY900014 groups. Furthermore, this finding could also explain the observation that the hypoglycaemia rate was lower in the Humalog group of subjects aged 3–<6 years in comparison to older children and adolescents in the Humalog group. However, an analysis on hypoglycaemic events <3.0 mmol/L (54 mg/dL) included in the CSR for the same age group yielded seemingly discrepant results from the currently submitted analysis, with markedly higher mean baseline event rate of hypoglycaemia (calculated per year) in the Humalog group. The MAH was requested to discuss and clarify the differences between the analyses in the response and the CSR. The MAH explained in the response to the second RSI that the discrepancy was due to a programming error in the analyses included in the CSR, which had been corrected in the analyses submitted with the response to the first RSI. In the response analysis, the hypoglycaemia rate (events/patient/year) during the lead-in period, when all subjects received Humalog

as prandial insulin (i.e., prior to randomisation), was 12.2 in the Humalog group, 52.1 in the LY900014 group and 61.2 in the LY900014 postmeal group. The MAH was further requested to perform a comprehensive analysis of hypoglycaemic events to exclude errors caused by the identified programming error. The updated analyses received with the MAH's response to the third RSI confirmed the previously drawn conclusions on the risk for hypoglycaemia. There were only minor numerical differences to originally submitted results. All results presented in this AR have been updated according to the MAH's response to third RSI.

The MAH submitted further analyses on the rate of hypoglycaemia in the age group <6 years compared with other age groups and with Humalog in the response to the first RSI. These analyses identified two children with a very high rate of hypoglycaemic events <3.0 mmol/L (54 mg/dL), one in the LY900014 group and one in the LY900014+20 group. The outliers could be considered as responsible for the remaining 2-fold difference in hypoglycaemia risk after adjusting for baseline rate and achieved HbA1c.

Overall, the number of subjects aged 3 to <6 is very low, hence, the data are scarce and the differences in hypoglycaemic events seem to be due to chance and not by differential PD of Lyumjev and Humalog in children <6 years of age. The MAH did not consider the need for addition of any warnings regarding hypoglycaemia risk in this age group to be warranted, and this is agreed with. In the entire study population, only 6 patients (LY900014, n=3; Humalog, n=3) experienced an episode of severe hypoglycaemia; and no difference was seen in total hypoglycaemic event rate between treatments.

In the CGM Addendum of ITSB, consistent with the known faster time-to-action profile of LY900014, the rate and incidence of post-dose hypoglycaemia was higher for LY900014 compared to Humalog at ≤1 and ≤2 hours and lower for LY900014 compared to Humalog at >4 hours after the prandial dose. Time spent in hypoglycaemia (<3.0 mmol/L [70 mg/dL] seems numerically higher especially during daytime in the LY900014+20 group (34.7 minutes) than the two other groups (28 and 25 minutes in the LY900014 and the Humalog group, respectively) (Figure 33). However, the differences between treatments in the rate and incidence of postprandial hypoglycaemic events were overall small from a clinical point of view.

No treatment differences for time spent in hypoglycaemic or hyperglycaemic ranges were seen in the CGM Addendum of ITSB. However, lack of study power caused by insufficient enrolment in the CGM Addendum prevents definitive interpretation of the CGM data.

Similar to adult trials with LY900014, the incidence of injection site reactions was markedly higher in subjects administered LY900014 than Humalog. The reactions were reported as injection site reaction, injection site erythema or injection site pain. However, whereas in adult trials the difference in injection site reactions was >10-fold between LY900014 and Humalog, in study ITSB the difference was around 3-fold: injection site reactions were reported for 8 subjects (2.7%) in the Humalog group, 22 subjects (7.9%) in the LY900014 group, and 4 subjects (2.9%) in the LY900014+20 group. All reported injection site reactions were mild or moderate, but two subjects discontinued LY900014 due to these reactions.

No difference between treatments was observed in immunogenicity. The majority of subjects (71.9%) were positive for pre-existing anti-insulin-lispro antibodies (ADA) at baseline, and 96.8 % of subjects were positive for ADA cross-reactive to native insulin. No clinically meaningful differences were seen in treatment-emergent ADA (TEADA), and there was no implication of effect of TEADA on efficacy or hypersensitivity.

2.5.10. Conclusions on clinical safety

Overall, the safety profile of LY900014 in children and adolescents is consistent with the known safety profile of Lyumjev in adult subjects. Treatment with LY900014 carries an overall similar risk for

hypoglycaemia as treatment with Humalog, but with an earlier postprandial timing of hypoglycaemic events due to faster time-to-action-profile of LY900014.

In children aged 3 to <6 years, hypoglycaemia below 3 mmol/L (54 mg/dL) occurred more frequently with LY900014 than Humalog. However, the data are scarce for this age group and the observed difference seems to be due to different baseline hypoglycaemia rate between study arms, different change in HbA1c, and two outliers with very high hypoglycaemia rate. Consequently, the differences seem to be due to chance in the very small group of subjects aged 3 to <6 years. No data are available for subjects below the age of 3 years, but since there is no reason to assume differential PD effect of LY900014 in subjects aged <3 years vs. >3 years, the results on safety can be extrapolated to children aged 1 to <3 years.

No other new safety concerns were identified. Similar to adults, injection site reactions are several-fold more frequent with LY900014 compared to Humalog in children and adolescents, too. These reactions are mild to moderate but do sometimes lead to discontinuation of treatment.

From a safety point of view, the B/R of Lyumjev is positive in children and adolescents aged 1 year and above.

In addition, the MAH should submit the following safety data in the next PSUR: hypoglycaemias in the age group 1 to <6 years.

2.5.11. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 12.1 with this application. The (main) proposed RMP changes were the following:

- Updates to the Product Overview: Proposed Indication for Lyumjev to improve glycaemic control in paediatric patients with diabetes mellitus.

Part I: Table Part I-1

- The addition of the proposed indication in paediatric patients.

Part II: SI

- The addition of data for the paediatric population. In addition, data for diabetes mellitus in general has been updated.

Part II: SIII

- The addition of Phase III clinical trial exposure data in paediatric patients. In addition, Phase III clinical trial exposure data for diabetes mellitus in general has been updated.

Part II: SIV.3

- Table SIV.2 has been updated with data for the paediatric population. The data on patients with CV impairment has been amended.

Part II: SV.1

- Post-authorisation exposure data has been updated.

No new safety concern has been identified.

Regarding the pharmacovigilance plan, no new additional pharmacovigilance activities have been proposed, which is endorsed.

No new additional risk minimisation measures have been added either, which is also considered acceptable.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

2.7. Summary of the safety concern

Table 45: Summary of the Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Severe hypoglycaemia, as a result of incorrect or incomplete data provided to a compatible software application is an important potential risk for the Tempo Pen
Missing information	None

2.8. Pharmacovigilance plan

Table 46: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Post-approval safety surveillance programme *Planned*	The objective of the blood glucose data assessment is to characterise the frequency of hypoglycaemia among patients using a compatible software application for Tempo Pen and to contextualise findings using an appropriate comparator population	Important Potential Risk for the Tempo Pen: Severe hypoglycaemia, as a result of incorrect or incomplete data provided to a compatible software application	Draft protocol	Within 6 months of first commercialisation
			Annual review summaries with the PSUR[a]	To be submitted for the subsequent 2 years following commercialisation
			Final Study Report	Within 3 years of first commercialisation

Abbreviation: PSUR = Periodic Safety Update Report.

[a] Analysis will begin after a connected system is commercially available and enough data for meaningful analysis are collected and will continue for 2 years after the connected system is available on the EU market.

2.9. Risk minimisation measures

Only routine risk minimisation measures are in place to manage the established safety profile and established risks. No specific wording is included to address the important potential risk of severe hypoglycaemia specifically in relation to the Tempo Pen.

Table 47: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Severe hypoglycaemia, as a result of incorrect or incomplete data provided to a compatible software application	Routine risk minimisation measures: Section 4.2 of the SmPC advises that when using the Tempo Pen, Smart Button and App, the patient should be instructed to check their blood sugar levels when considering or making decisions about another injection if they are unsure how much they have injected. Section 4.4. of the SmPC already includes extensive advice on the detection and management of hypoglycaemia in patients treated with insulin lispro. These recommendations are not exclusive to the Tempo Pen. Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Follow-up forms specific to severe hypoglycaemia as a result of incorrect or incomplete data provided to a compatible software application in the use of the Lilly connected system* Additional pharmacovigilance activities: *Statistical analysis of secondary observational data to evaluate blood glucose values from Tempo Pens versus a relevant nonconnected comparator diabetic population*

2.10. Update of the Product information

As a consequence of this new indication, sections 4.1, 4,2, 4.8, 5.1, and 5.2 of the SmPC have been updated to include indication for use and information on safety, efficacy, and PK/PD of Lyumjev in paediatric patients aged 1 year and above. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found unacceptable for the following reasons:

The MAH justifies absence of user consultation or bridging report by stating that the "*addition of the new indication targets a similar patient group and their parents or caregivers as the one that made up the representative test population for the performed user testing. The proposed text modifications to the package leaflet resulting from the addition of this new indication are minor and do not include text that is significantly different from that user tested*".

It is agreed that the structure and design of the revised Lyumjev Package Leaflets have not changed due to the new information and there are no changes which alter overall readability. However, the user tests on the Lyumjev PL submitted within the MAA were performed with only adult subjects: for the cartridge, user test with target group of adults aged 31 to 58 years; for KwikPen 100U/mL, a bridging report; for KwikPen 100 U/mL, user test with adults aged 20 to 66 years; and for the vial, user test with adults aged

21 to 57 years.

Hence, no readability testing has been performed with paediatric age groups. With growing age, a child with diabetes typically takes more and more responsibility of their insulin treatment, including, e.g. injections during school days. Many teenagers have full responsibility of their insulin treatment, some are not even living with their parents. The guideline on the readability of the labelling and package leaflet of medicinal products for human use (Rev.1, 12 Jan 2009) states the following general consideration: *"If the package leaflet is well designed and clearly worded, this maximises the number of people who can use the information, including older children and adolescents, those with poor literacy skills and those with some degree of sight loss."*

The MAH was requested to justify why results of the prior PL readability tests conducted in adults could be extrapolated to paediatric age groups and parents/caregivers of children, who were not included in the target groups of the tests. In their response to the first RSI, the MAH has justified that no further testing of the Lyumjev PL or device are needed to be performed, since readability tests and human factor studies in children and adolescents were performed on the Humalog KwikPen and Humalog Junior KwikPen presentations, which are similar to the corresponding Lyumjev presentations. It is agreed that the results of these Humalog tests can be extrapolated to Lyumjev.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Type 1 diabetes mellitus (T1D) is one of the most common chronic diseases in children and adolescents. A great majority of paediatric subjects with diabetes suffer from T1D and have subtotal or total loss of insulin secretion. In adolescents, type 2 diabetes mellitus (T2D) is occurring more and more frequently in those with obesity and in high-risk ethnic populations. However, T2D remains relatively rare in the general European population. Both types of diabetes carry a risk for chronic complications caused by hyperglycaemia.

With this application the MAH seeks to extend the indication for Lyumjev to include children and adolescents from the age of 1 year.

3.1.2. Available therapies and unmet medical need

Children and adolescents with T1D are dependent on daily and lifelong insulin treatment. T1D is in general treated by a multiple-dose insulin (MDI) regimen or continuous subcutaneous insulin infusion (CSII) via an insulin pump to mimic physiological insulin secretion as closely as possible.

T2D is typically managed with diet, exercise, oral antihyperglycemic medications, GLP1 receptor agonists, and sometimes exogenous insulin.

Both types of diabetes are associated with long-term complications caused by chronic hyperglycaemia. In T2D, obesity-associated metabolic disturbances linked to insulin resistance increase the risk for complications. Several long-term studies in both T1D and T2D have demonstrated that long-term diabetic complications can be reduced by successful treatment of hyperglycaemia.

Aggressive treatment of hyperglycaemia carries along the risk for hypoglycaemia, which can be severe and life-threatening. The challenge to obtain good glycaemic control in the absence of hypoglycaemia is greater in a paediatric population compared to an adult population due to growth, more variable lifestyle, need of assistance with insulin injections, and hormonal changes. Changes in eating and physical activity are also less predictable in paediatric patients.

LY900014 provides another treatment option for paediatric patients with diabetes. LY900014 more closely mimics endogenous insulin action compared to Humalog. However, there is already on market another faster-acting mealtime insulin, faster-acting aspart, authorised for use in patients aged 1 year and above.

Preferably, mealtime insulin bolus doses should be administered prior to meals for optimal timing of the peak effect of insulin with the postprandial glycaemic excursion. However, flexibility in dose timing (up to 20 minutes after a meal) provided by LY900014 is also important for young children with diabetes due to unpredictable eating, which hampers defining the correct insulin dose for the meal.

3.1.3. Main clinical studies

Study ITSB was a 26-week, Phase 3, prospective, randomized, outpatient, multinational, multicentre, parallel, active-controlled study conducted in paediatric patients (age range 3 to <18 years) with T1D currently using an MDI regimen. The study was designed to test the hypothesis that LY900014 is noninferior to Humalog on glycaemic control (change in HbA1c) as the primary endpoint. Two secondary gated objectives were 1) to test the hypothesis that LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal (LY900014+20) is noninferior to Humalog, administered as prandial insulin (0 to 2 minutes prior to the meal), on glycaemic control, and 2) to test the hypothesis that LY900014 is superior to Humalog in improving glycaemic control (HbA1c) when administered as prandial insulin (0 to 2 minutes prior to the meal).

A subset of subjects in ITSB participated in a substudy, "CGM addendum", evaluating the 24-hour glucose profile captured with Dexcom G6® CGM System (Dexcom G6) for LY900014 and Humalog. The primary objective of the CGM Addendum was to compare the iAUC0-2 hours after the start of meals between the two treatments. Due to unsuccessful recruitment, this voluntary substudy was not powered to show a difference between LY900014 and Humalog.

Data form ITSB is presented for 716 randomised subjects, of whom 298 in the Humalog group, 280 in the LY900014 group, and 138 in the LY900014+20 group. Of the subjects, none were <3 years, 27 were aged 3 to <6 years, 226 aged 6 to <12 years, and 463 aged 12 to <18 years. The demographic and baseline characteristics were balanced between groups. A high proportion of subjects completed the trial: 96.6% of the Humalog group, 95% of the LY900014 group, and 97.8% of the LY900014+20 group.

3.2. Favourable effects

The study ITSB met its primary objective, since non-inferiority of LY900014 to Humalog, both administered within 0-2 minutes prior to meal, was demonstrated with the relevant NIM for EU, 0.3% (3 mmol/mol). Non-inferiority of LY900014 versus Humalog in change from baseline in HbA1c at Week 26 was demonstrated for both the efficacy estimand and ITT estimand (efficacy estimand: LSM Difference [95% CI] = -0.02 [-0.17, 0.13]; ITT estimand: LSM Difference [95% CI] = -0.01 [-0.15, 0.14]). It is noteworthy that no improvement in mean glycaemic control was observed from baseline to 26 weeks in any of the treatment arms.

Of the two multiplicity-controlled secondary endpoints, superiority of LY900014 vs. Humalog in controlling glycaemia (change in HbA1c from baseline) was not met. However, the other multiplicity-controlled

secondary endpoint was met: postprandially (within 20 minutes from start of meal) administered LY900014 was non-inferior to preprandial Humalog (within 0-2 minutes before meal) in terms of change in HbA1c.

The proportion of patients with HbA1c <7% and <7.5% at Week 26 were similar in all three arms of the study. At Week 26, approximately 20% of patients achieved the HbA1c target <7% in all three study groups.

In comparison to Humalog, LY900014 reduced postprandial glucose levels as measured by a 7-point self-monitoring of blood glucose (SMBG) profile, which is an expected finding for an insulin with a known faster time-to-action profile. Since the analyses on postprandial glucose were not controlled for multiplicity, any references to statistical significance are considered as nominal and not indicative of true difference in a confirmatory sense. The LS mean change from baseline at week 26 in the daily mean postprandial glucose excursion at 1 hour was −0.6 mmol/L (−11.2 mg/dL) with LY900014 compared to 0.1 mmol/L (1.3 mg/dL) with Humalog; with a LSM difference of −0.7 mmol/L (95% CI −1.0, −0.4) [−12.5 mg/dL (95% CI −17.5, −7.6)].

Postprandial glucose excursions according to SMBG were numerically higher when LY900014 was dosed after the meal. The LS mean difference in change from baseline in 1-hour PPG excursion between premeal and postmeal administered LY900014 was 0.5 mmol/L (95% CI 0.1, 0.9) [8.9 mg/dL (95% CI 2.2, 15.5)] in favour of premeal vs. postmeal administration of LY900014.

No differences were observed between treatments in daily mean bolus, basal or total insulin dose at week 26.

The substudy investigating HRQoL demonstrated no differences between study arms as measured by the PedsQL questionnaire. This finding is concordant with pivotal trials in adults, which also failed to demonstrate any benefit on HRQoL by LY900014.

3.3. Uncertainties and limitations about favourable effects

Data in for patients under the age of 6 years in study ITSB is overall scarce. Only 27 patients, of whom 10 in the LY900014 group and 10 in the LY900014+20 group, participated in the study. Of note, no subjects below the age of 3 years were included in the study.

There seems to be a numerical trend for increase in HbA1c during the first 12 weeks of the study in the LY900014 and LY900014+20 groups compared with the Humalog group. However, the difference is no longer evident at Week 26. Since the differences between treatments at each measurement point during the study were not significant, this issue is not pursued further.

The analyses on PPG excursions based on SMBG (see above in Section 3.2) in paediatric subjects were not controlled for multiplicity.

Unfortunately, the substudy CGM addendum of ITSB was unpowered to demonstrate differences between study arms due to recruitment problems and consequent low number of subjects. Hence, even though the primary endpoint of $iAUC_{0\text{-}2hours}$ after all meals was numerically better for LY900014 vs. Humalog, no firm conclusions can be drawn from this finding. Additionally, robust data on time in glycaemic target glucose level are not available due to lack of power. No relevant difference was observed in time in glucose range 3.9 to 10.0 mmol/L (70 to 180 mg/dL) between LY900014 and Humalog; both groups spent <50% time in this range.

3.4. Unfavourable effects

There were no deaths reported in study ITSB. There was a total of 20 patients who reported serious adverse events (SAEs) during the study, with a higher number of SAEs in the Humalog treatment group: Humalog, n=12 (4.0%), LY900014, n=6 (2.1%), and LY900014+20, n=2 (1.4%). SAEs reported by more than 1 patient from randomization to safety follow-up were hypoglycaemia (Humalog, n=2; LY900014, n=3; LY900014+20, n=0) and diabetic ketoacidosis (DKA, Humalog, n=0; LY900014, n=2; LY900014+20, n=1). All 3 events of DKA were assessed by investigator to be due to non-administration of insulin according to prescribed guidelines or omission of insulin dosing and unrelated to study drug. All 3 events resolved following treatment with full recovery.

The overall rate and incidence of hypoglycaemia observed in paediatric patients in Study ITSB with LY900014 treatment was similar compared to Humalog and consistent with the hypoglycaemia findings in adult patients with diabetes who were treated with LY900014. A total of 6 patients (LY900014, n=3; Humalog, n=3) experienced an episode of severe hypoglycaemia. However, in subjects aged 3 to <6 years, the rate of hypoglycaemia below BG <3.0 mmol/L (54 mg/dL) was 3−4-fold higher in the LY900014 and LY900014+20 group than in the Humalog group. Compared with older children and adolescents, the 3 to <6-year-old subjects had a lower rate of hypoglycaemia in the Humalog group but a higher rate of hypoglycaemia in the LY900014 and LY900014+20 groups. No data are available for subjects aged <3 years.

Similar to adult trials with LY900014, the incidence of injection site reactions was markedly higher in subjects administered LY900014 than Humalog. However, whereas in adult trials the difference in injection site reactions was around 10-fold between LY900014 and Humalog, in study ITSB the difference was around 3-fold in comparison to Humalog. All reported injection site reactions were mild or moderate; however, 2 subjects discontinued study drug due to injection site reactions.

No difference was observed in immunogenicity between LY900014 and Humalog.

3.5. Uncertainties and limitations about unfavourable effects

The information on the risk for hypoglycaemia in paediatric subjects is scarce and insufficient for assessment of the clinical relevance of the observed markedly higher risk for hypoglycaemia below 3.0 mmol/L (54 mg/dL) in subjects aged from 3 to <6 years. Furthermore, no data are available for subjects below the age of 3 years. The MAH was requested to further analyse and discuss the observed excess risk for hypoglycaemia in this age group. Additional analyses by the MAH showed that this difference was reduced but was still more than 2-fold after adjusting for baseline hypoglycaemic rate and achieved HbA1c level at Week 26. Moreover, the MAH identified two individual subjects, one in the LY900014 group and one in the LY900014+20 group, whose high rate of hypoglycaemic events may have partly driven the difference seen between these treatment regimens vs. Humalog, which is interpreted to account for the remaining risk after the adjusted analysis, based on a scatter plot with the outliers excluded from the analysis.

Overall, the submitted analyses indicate that the difference is likely due to chance.

A discrepancy was noticed regarding results on hypoglycaemic events at baseline (i.e., during the lead-in period) reported in the interim CSR and in the response to the first RSI. In the interim CSR, in children aged 3 to <6 years, a markedly higher mean baseline event rate of hypoglycaemia was given for the Humalog group compared with the other two groups, whereas the model-based estimates in the response to the first RSI indicated lower baseline event rate of hypoglycaemia with Humalog as compared with the LY900014 and LY900014+20 groups. The MAH clarified in their response to the second RSI that the discrepancy was due to a programming error identified prior to database lock but not corrected for in the analyses for the interim CSR. However, analyses submitted with the first and second response to LoQ were

correct. This programming error affected 9 patients in the full study population. For 7 patients, the baseline event rate was inflated because of the incorrect shortened duration (lead-in period start date was the same as the end date). For 1 patient in the 3 to less than 6 years of age cohort who received Humalog, the event rate for glucose less than 54 mg/dL (3.0 mmol/L) was incorrectly calculated as 730.5 events per year, but once corrected, it was reduced to 26.1 events per year. This patient had a significant impact on the Humalog group mean.

For the two patients with post-baseline data errors, there was, according to the MAH, negligible impact on the event rate because very few hypoglycaemic events were reported, and once the total duration was corrected, the rate was essentially the same. The MAH stated that this programming error had negligible impact on the overall results (p-values and LS means) and conclusions of the post-baseline event rates because the statistical model did not include baseline hypoglycaemic rate.

The updated subgroup analyses for glucose less than 54 mg/dL (3.0 mmol/L) for the full study population were submitted with the MAH's response to the second RSI. However, all analyses on hypoglycaemic events and tables and figures thereof in the CSR were not repeated and submitted by the MAH with either response to first or second RSI. Therefore, the MAH was requested to perform all analyses on hypoglycaemic events included in the CSR for the total study population and subgroups with the correct numbers and submit the updated texts, figures and tables concerning hypoglycaemia. The requested analyses were received with the MAH's response to the third RSI. There were several but minor numerical changes in the results. None of the repeated analyses revealed any findings of clinical importance that would change the conclusions regarding risk for hypoglycaemia in paediatric patients.

3.6. Effects Table

Effects Table for LY900014 (Lyumjev), Paediatric Population. Phase 3, MDI Study I8B-MC-ITSB (Data Cutoff Date: 16 July 2021; Efficacy Estimand)

Effect	Short description	Unit	Treatment	Control		Uncertainties / Strength of evidence
			Mealtime LY900014	**Mealtime Humalog**	**LSM Diff (95% CI)**	Non-inferiority of premeal Lyumjev (LY900014) vs. premeal Humalog demonstrated. Superiority not demonstrated.
HbA1c change	LS Mean (SE) CFB at 26 wks	%	0.06 (0.05)	0.09 (0.05)	-0.02 (-0.17, 0.13)	
		mmol/mol	0.71 (0.59)	0.94 (0.57)	-0.23 (-1.84, 1.39)	
			LY900014+20	**Mealtime Humalog**	**LSM Diff (95% CI)**	Non-inferiority of postmeal Lyumjev (LY900014+20) vs. premeal Humalog demonstrated
HbA1c change	LS Mean (SE) CFB at 26 wks	%	0.07 (0.08)	0.09 (0.05)	-0.02 (-0.20, 0.17)	
		mmol/mol	0.77 (0.83)	0.94 (0.57)	-0.17 (-2.15, 1.81)	

			Mealtime LY900014	**Mealtime Humalog**	**LY900014+20**	
Severe hypoglycaemia, randomisation to Wk 26	Aggregate rate per 100 years		2.20	2.04	0.00	
	Incidence (n [%])		3 (1.1)	3 (1.0)	0 (0.0)	
All documented hypoglycaemia with BG ≤3.9 mmol/L (≤70 mg/dL) and BG≤3.0 mmol/L (≤54 mg/dL)	Rate and incidence		• BG <3.0 mmol/L (<54 mg/dL) rate and incidence were similar across treatment groups. • BG ≤3.9 mmol/L (≤70 mg/dL) rate was similar across treatment groups. • BG ≤3.9 mmol/L (≤70 mg/dL) incidence was similar between LY900014 and Humalog. The incidence was lower for LY900014+20 compared with Humalog: o LY900014+20: n = 121 (87.7%) and o Humalog: n = 280 (94.0%).			In subjects aged from 3 to <6 years, significantly more documented clinically significant hypoglycaemia (BG <3.0 mmol/L) with LY900014 and LY900014+20 compared to Humalog: RR 3.37 [95% CI 1.68, 6.76] for LY900014 (n=10) vs. Humalog (n=7), and RR 4.19 [95% CI 1.87,9.36] for LY900014+20 (n=10) vs. Humalog. No data <3 years of age.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Injection site reactions	Number and percentage of patients that experienced ≥1 TEAE of injection site reactions		A total of 46 TEAE of injection site reactions /34 patients (4.7%). All were mild and moderate in severity. More patients in the LY900014 group experienced ≥1 injection site reaction TEAE: o Humalog, n = 8 patients (2.7%) o LY900014, n = 22 patients (7.9%), and o LY900014+20, n = 4 patients (2.9%). Two patients in the LY900014 treatment group discontinued study treatment due to AEs of injection site reactions.		The finding is in line with pivotal study data from adult subjects (See SmPC).

Abbreviations: AE = adverse event; BG = blood glucose; CFB = change from baseline; CI = confidence interval; HbA1c = haemoglobin A1c; LSM = least square mean; n = number of patients; SE = standard error; TEAE = treatment-emergent adverse event. a) Mealtime = Study drug administered 0 to 2 minutes prior to the start of the meal; LY900014+20 = LY900014 administered 20 minutes after the start of the meal (Postmeal).

Note: The analyses for the primary and multiplicity-adjusted objectives were performed for the efficacy estimand including data collected prior to permanent discontinuation of study drug and for the ITT estimand including all data collected regardless of study drug use. For the EU submission, the primary analysis has been presented in this Clinical Overview using the efficacy estimand.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

LY900014 was shown to be non-inferior to Humalog in paediatric age groups: the mean HbA1c (%/mmol/mol) at Week 26 was 7.88/62.57, 7.85/62.35 and 7.86/62.41 in the Humalog, LY900014, and LY900014+20 groups, respectively (efficacy estimand).

Superiority of LY900014 vs. Humalog in controlling glycaemia (change in HbA1c from baseline) was not met. Administering LY900014 within 20 minutes from start of meal was demonstrated noninferior to Humalog administered within 0-2 minutes before meal. No data are available for subjects aged <3 years, and data on subjects <6 years of age is scarce. Nevertheless, there is no indication of differential efficacy based on age, since the HbA1c levels were similar in all paediatric age groups. From a pharmacological point of view, similar efficacy is expected also in patients below the age of 3 years.

Administering LY900014 after meal was not as efficacious as premeal administration for glucose control during the early postprandial period. However, in light of the similar HbA1c achieved in groups administering LY900014 premeal and postmeal, postprandial administration can be accepted as an option in situations when the carbohydrate and energy content of the meal cannot be anticipated. Postprandial administration has been accepted for adults using Lyumjev and for all age groups using Humalog. This option is important especially for toddlers.

There was a 3−4-fold increased rate of documented, clinically relevant hypoglycaemia below 3.0 mmol/L (54 mg/dL) in subjects younger than 6 years in the LY900014 and LY900014+20 groups vs. Humalog group. After adjusting for baseline hypoglycaemia rate and for HbA1c at week 26, these differences remained >2-fold. No data are available for patients aged 1 to <3 years. The increased rate of hypoglycaemia in the age group of 3 to <6 years is not explained by overall glycaemic control, which was overall similar in terms of HbA1c at week 26. After exclusion of two outliers (one in the LY900014 group and one in the LY900014+20 group) with a very high hypoglycaemia rate, this difference in hypoglycaemic event rate between study groups is no longer seen.

The risk for injection site reactions is several-fold higher with LY900014 compared with Humalog. However, the difference between LY900014 and Humalog in the risk of injection site reactions was lower in paediatric subjects in study ITSB than was seen in adult pivotal trials. Moreover, these reactions were mild to moderate and rarely lead to discontinuation of LY900014.

Additional data in paediatric patients with T2D are not required as per *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* (CPMP/EWP/1080/00 Rev. 1), since the clinical efficacy, safety and PK/PD of Lyumjev (LY900014) has been characterised in paediatric patients with T1D and in adults with T1D and T2D; including similar PK/PD after single dose via SC injection and via CSII in adult and paediatric patients with T1D. Consequently, no paediatric efficacy and safety trial is deemed to be needed for approval of use of LY900014 in paediatric patients with T2D, in paediatric patients using CSII, or children aged 1 to <3 years. From a pharmacological point of view, similar efficacy and safety is expected also in patients below the age of 3 years.

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 paediatric T1D subjects aged from 3 to <18 years. No data are available for patients <3 years of age. Efficacy and safety of LY900014 have been characterised for paediatric patients

aged 6 years and older. For subjects below the age of 6 years, a 3−4-fold rate for documented, clinically relevant hypoglycaemia (<3.0 mmol/L, 54 mg/dL) was observed, and the rate remained >2-fold after adjusting for baseline hypoglycaemia and achieved HbA1c. However, the remaining difference is explained by two outliers with a very high rate of hypoglycaemia. It is however proposed that hypoglycaemias in the age group 1 to <6 years should be followed and reported in the PSURs. A programming error was identified by the MAH which compromised analyses on hypoglycaemic events. Updated analyses with correct data yielded only minor numerical differences compared to originally submitted results. None of the differences were of clinical relevance.

Clinical efficacy and safety of Lyumjev (LY900014) has been characterized in paediatric patients with T1D and in adults with T1D and T2D, including similar PK/PD after single dose via SC injection and via CSII in adult and paediatric patients with T1D. Hence, additional data in paediatric patients with T2D are not needed as per Guideline on clinical investigation *of medicinal products in the treatment or prevention of diabetes mellitus* (CPMP/EWP/1080/00 Rev. 1). Consequently, no paediatric efficacy and safety trial is needed for approval of use of LY900014 in paediatric patients with T2D or in paediatric patients using CSII. Efficacy and safety data can also be extrapolated to children aged 1 to <3 years.

As a conclusion, the B/R of Lyumjev in paediatric patients is positive.

3.7.3. Additional considerations on the benefit-risk balance

LY900014 is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Amglidia (glibenclamide).

The MAH withdrew their request on one additional year of market protection in their response to the first RSI.

3.8. Conclusions

The overall B/R of Lyumjev is positive for children and adolescents aged 1 year and above.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of diabetes mellitus in adolescents and children aged 1 year and above, based on final results from study I8B-MC-ITSB; this is a pivotal Phase 3 study designed to evaluate the safety and efficacy of Lyumjev compared to Humalog in combination with basal insulin in children and adolescent patients with T1D. The study was designed to compare change in HbA1c as the primary endpoint. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The

Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement update minor editorial and linguistic changes in the SmPC and Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Lyumjev is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.