Protocol I8B-MC-ITST (V2)

Effects of LY900014 on Recovery from Hyperglycemia Compared to Humalog in Subjects with Type 1 Diabetes Mellitus (T1DM) on Continuous Subcutaneous Insulin Infusion

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CLINICAL TRIAL PROTOCOL

Trial ID: I8B-MC-ITST

Effects of LY900014 on Recovery from Hyperglycemia Compared to Humalog in Subjects with Type 1 Diabetes Mellitus (T1DM) on Continuous Subcutaneous Insulin Infusion

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 22-Jan-2020 GMT

AGREEMENT ON THE PROTOCOL

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17 JAN 2020
Date

Sponsor Representative (Eli Lilly and Company):

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20-JAN-2020
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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{ins}	Area under the serum insulin concentration time curve
B	Bolus administration
BMI	Body mass index
CFBL	Change from baseline
CI	Confidence interval
C_{max}	Maximum serum insulin concentration
CRF	Case report form
CSII	Continuous Subcutaneous Insulin Infusion
ECG	Electrocardiogram
FAS	Full analysis set
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FSFV	First subject first visit
GCP	Good clinical practice
GD	Glucodynamics
GIR	Glucose infusion rate
γGT	Gamma-glutamyltransferase
HbA1C	N-(1-deoxy)-fructosyl-haemoglobin
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International conference on harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional review board
i.v.	Intravenous(ly)
LDH	Lactic dehydrogenase
LDL	Low-density lipoprotein
LS	Least squares
LSLV	Last subject last visit
mFAS	Modified Full analysis set
NIMP	Non-investigational medicinal product
PAH	Pulmonary arterial hypertension
PD	Pharmacodynamics

PG	Plasma glucose
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous(ly)
SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1DM	Type 1 Diabetes Mellitus
t_{max}	Time to maximum observed insulin concentration
TIF	Trial investigator file
U	Units

1 SYNOPSIS

Name of Sponsor: Eli Lilly and Company	**Trial ID:** I8B-MC-ITST
Title of the trial: Effects of LY900014 on Recovery from Hyperglycemia Compared to Humalog in Subjects with Type 1 Diabetes Mellitus (T1DM) on Continuous Subcutaneous Insulin Infusion	
Trial design: Single center, randomized, 2-treatment, subject- and investigator-blind, 2-period cross-over trial in subjects with T1DM.	
Clinical phase of development: Phase I	
Trial centre: Profil Mainz GmbH & Co. KG, Malakoff-Passage, Rheinstr. 4C, D-55116 Mainz, Germany	
Principal Investigator: PPD Profil Mainz GmbH & Co. KG, Malakoff-Passage, Rheinstr. 4C, D-55116 Mainz, Germany	
Planned trial start (First Subject First Visit): February 2020	**Planned trial end (Last Subject Last Visit):** June 2020
Trial population: Subjects with diabetes mellitus type 1 on continuous subcutaneous insulin infusion (CSII)	
Key Objectives: The aim of the study is to compare the time to recovery from hyperglycemia following LY900014 administration in comparison to Humalog® in a similar situation as when a subject experiences hyperglycaemia by forgetting to deliver a bolus after consuming a meal or when there is suspension of insulin delivery e.g. due to a malfunction of the insulin pump. **Primary objective:** • To compare the time to recovery from hyperglycaemia following a missed meal bolus with LY900014 vs. Humalog®, given as a correction bolus via pump infusion • To compare the time to recovery from hyperglycaemia following basal insulin suspension with LY900014 vs. Humalog®, given as a correction bolus via syringe injection **Secondary objectives:** • To compare the pharmacodynamic and insulin lispro pharmacokinetic following a correction bolus of LY900014 vs. Humalog® during recovery from hyperglycaemia after a missed meal bolus. • To compare the pharmacodynamic and insulin lispro pharmacokinetic following a correction bolus of LY900014 vs. Humalog® during recovery from hyperglycaemia after basal insulin suspension. • To assess the safety and tolerability of LY900014 and Humalog.	
Key Endpoints: **Primary Endpoint(s):** • Time to recovery from hyperglycemia **Secondary Endpoints:** *PG* • $AUC_{(B\text{-}tPG140)}$ • $AUC_{(B\text{-}tPG180)}$ • Rate of change in PG	

- PG_{max}

PK

- t_{max}
- Early 50% t_{max}
- $AUC_{(0\text{-}15min)}$
- $AUC_{(0\text{-}30min)}$

Safety:

- Adverse events

Key inclusion and key exclusion criteria:

Key inclusion criteria

- Signed and dated informed consent obtained before any trial-related activities.
- Male or female subjects with type 1 diabetes.
- Age between 18 and 64 years, both inclusive.
- Body Mass Index (BMI) between 18.5 and 30.0 kg/m^2, both inclusive.
- HbA1c <= 8.5%.
- Using CSII and stable insulin regimen for at least 3 months prior to inclusion into the trial.

Key exclusion criteria

- Known or suspected hypersensitivity to IMP(s) or related products.
- Receipt of any medicinal product in clinical development within 30 days before randomization in this trial.
- Known slowing of gastric emptying and or gastrointestinal surgery that, in the opinion of the investigator, might change gastrointestinal motility and food absorption.
- Proliferative retinopathy or maculopathy as judged by the Investigator based on a recent (<1.5 years) ophthalmologic examination.Widespread subcutaneous lipodystrophy in the abdomen.
- Current use of any glucose-lowering agents other than insulin within 3 months prior to screening. .
- Chronic or recent use of corticosteroids.

Sample size:

Up to 28 subjects are planned to be randomised so that at least 24 complete the trial

Investigational Medical Products:

Test product:

Insulin lispro (LY900014), vials 100 U/mL, for subcutaneous administration (infusion via pump and injection via syringe).

Reference product:

Insulin lispro (Humalog®), vials 100 U/mL, for subcutaneous administration (infusion via pump and injection via syringe).

Duration of treatment:

Subjects will receive each IMP for approximately 48 hours during two separate study visits. The IMP will be administered subcutaneously both via an insulin pump (continuous subcutaneous insulin infusion, CSII) and via a syringe injection.

Assessments:

The trial includes an information visit (Visit 0), a screening visit (Visit 1), two in-house study visits with IMP administration (Visits 2 and 3), and a follow–up visit (Visit 4).

The information visit will take place at least 1 day prior to the screening visit in order to obtain the subjects informed consent. The subjects will attend the screening visit 1–28 days prior to Visit 2 to determine their eligibility. After screening, all eligible subjects will, in random order, undergo two in-house study visits. Each in-house visit will comprise a 3-day stay at the trial site. The in-house visits

will be separated by a wash-out period of 3–14 days (between Visit 2, Day 2 and Visit 3, Day 1). Each subject will be randomised to a treatment sequence consisting of two treatments, i.e. LY900014 and Humalog®, to be administered at the two separate in-house study visits. Randomization will take place on Day -1 of Visit 2.

At each of the two in-house visits, subjects will arrive at the trial site in the afternoon of Day -1. After a check of continued eligibility, the subjects own insulin pump will be disconnected and subjects will receive a study pump filled with IMP (Medtronic 640G). A new infusion set will be inserted into the abdominal wall. The subject's usual basal rate settings will be programmed in the study pump and the basal rate infusion will be started.

Day -1 / Day 1: recovery from hyperglycemia after missed meal bolus

In the evening of Day -1, subjects will receive a pre-defined evening meal. The subjects will cover the meal with a bolus administered by the study insulin pump. Overnight, the basal insulin infusion rate will be running and a target fasting plasma glucose level in the range of 126 ± 20 mg/dL will be aimed for. A single hourly basal rate will be started from at least – 3 hours prior to meal ingestion. At approx. 08:00 hours on Day 1, a standard liquid meal CCI will be provided. No bolus insulin will be administered with the aim to induce postprandial hyperglycemia (PG > 240 mg/dL). On-site glucose measurements CCI will be performed regularly and frequently after meal ingestion. As soon as a glucose measurement above the high glucose threshold (PG > 240 mg/dL) has been measured and the result has been confirmed by a second measurement, a correction bolus will be administered with the aim to bring the subject's glucose level down to PG ≤ 140 mg/dL. Regular and frequent sampling for glucose on-site analysis continues and the time to reach the euglycemic range threshold will be documented. PK and glucose measurements will be collected until 5 hours after administration of the correction bolus. In case PG < 54 mg/dL, hypoglycemia rescue will be provided. In case PG > 306 mg/dL for more than one hour, hyperglycaemia rescue will be provided. Thereafter, subjects will receive a free-choice lunch and a pre-defined evening meal covered by the subject's usual bolus dose.

Day 1 / Day 2: recovery from hyperglycemia after basal insulin suspension

After the insulin bolus given with the evening meal, no correction boli should be given subcutaneuously. Overnight, the basal insulin infusion rate will be running and a target fasting plasma glucose level in the range of 126 ± 20 mg/dL will be aimed for. The basal insulin infusion rate will be fixed to a single hourly rate from at least – 3 hours prior to basal insulin suspension. Basal insulin suspension will be performed between 8 and 10 hours after the dinner meal on Day 1. On-site glucose measurements CCI will be performed regularly and frequently to follow the rise in plasma glucose concentration above 240 mg/dL and blood samples for PK analysis will be taken to analyse the decline in circulating insulin levels. As soon as a glucose measurement above the high glucose threshold has been measured and the result has been confirmed by a second measurement a correction bolus will be administered via a subcutaneous injection in the periumbilical region using an insulin syringe. In addition, a plasma sample for ketone concentration will be taken during this time. Regular and frequent sampling for PK, ketone and glucose analysis continues and the time to reach a PG ≤ 140 mg/dL will be documented.

After completion of basal insulin suspension procedures at Visit 3 Day 2, subjects will be switched back to their usual diabetes therapy and come back to the trial centre for the final examination.

Statistical methods:

A sample size of up to 28 patients with T1DM will be enrolled and at least 24 subjects should complete this trial to achieve study objectives. The sample size is considered sufficient to evaluate a difference in the primary endpoint between the treatments of 32 minutes with a power of 80%. Discontinued subjects may be replaced to ensure that 24 subjects complete the trial. A replacement subject will be assigned to the same treatment sequence as the subject being replaced. .

Primary statistical analyses will be conducted on the set of subjects who complete the study according to the sequence/treatment to which they are randomized. Subjects who did not keep identical insulin lispro doses for LY900014 and Humalog/or had difference in the comsumption of the meal for each day and period will be excluded from the statistical analysis of the PK/GD parameters. Safety analyses will be conducted for all enrolled subjects, whether or not they complete all protocol requirements.

Primary GD endpoint:

Time to recovery from hyperglycemia (time of correction bolus to time when PG = 140 mg/dL, will be determined based on PG measurements. Exact points of intersection with PG of 140 mg/dL will be determined using linear interpolation. Comparisons between the treatments will be peformed per day using a mixed-effect model with raw endpoint as response, treatment, period and sequence as fixed effects and subject within sequence as a random factor. Within the model, least squares means of LY900014 and Humalog®, differences in least squares means and the corresponding 95% CI for the treatment difference will be estimated. The p-value on the difference between least squares means will be used to determine statistical significance. The treatment ratio and 95% CI for the ratio will be calculated using Fieller's theorem.

Secondary GD Endpoints:

Secondary GD endpoints will be analysed per day using a multiplicative linear mixed model ANOVA with treatment, period and sequence as fixed effects and subject within sequence as a random factor. A multiplicative linear mixed model (log-transformed response variable) will be used for AUC endpoints and PGmax. Treatment ratios and corresponding 95% CIs will be determined. An additive model (untransformed response variable) will be used for rate of change in PG and time parameters. Treatment ratios and 95% CIs will be calculated by Fieller's method.

Secondary PK Endpoints:

Secondary PK endpoints will be analysed per day using a linear mixed model with treatment, period and sequence as fixed effects and subject within sequence as a random factor. A multiplicative linear mixed model (log-transformed response variable) will be used for AUC endpoints. Treatment ratios and corresponding 95% CIs will be determined. An additive model (untransformed response variable) will be used for time parameters. Treatment ratios and 95% CIs will be calculated by Fieller's method.

Safety endpoints:

All adverse events will be listed and summarised by descriptive statistics. All serious adverse events will be reported.

2 SCHEMATIC TRIAL OVERVIEW

2.1 Chronological Structure of the Trial

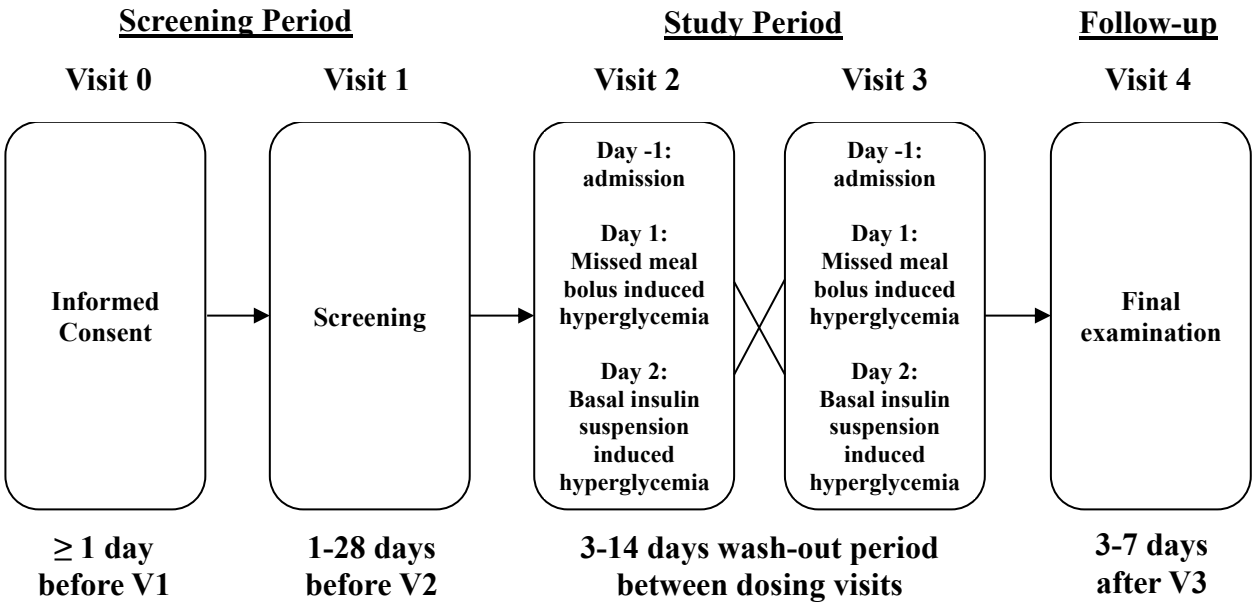

Figure 1 Schematic overview of the chronological structure of the trial

2.2 Trial Flow Chart

The trial flow chart is the master representation of the trial schedule. In case of (apparent) inconsistencies in the trial protocol the information provided here is the binding one.

Table 1 Trial Flow Chart

Trial Period	**Screening Period**		**Treatment Period 1 and 2**			**Follow-up**
Visit no.	**0**	**1**	**2 and 3**			**4**
	Informed Consent	**Screening**	**Induced hyperglycemia and recovery**			**Final examination**
Timing	≥ 1 day before Visit 1	1-28 days prior to Visit 2	3-14 days between Visit 2 and Visit 3			3-7 days after Visit 3
Day			Day -1	Day 1	Day 2	
In-house Visit/Period			X	X	X	
Informed consent	X	X[1]				
Fasting		X		X	X	X
Inclusion/exclusion criteria		X	X[2]			
Demographic data		X				
Smoking and alcohol consumption habits		X				
Concomitant illness and medical history		X				
Weight, height, BMI		X	X[3]			X[3]
Alcohol breath test		X	X			
Physical examination		X	X		X	X
Vital signs		X	X		X	X
12-lead ECG		X				X
Haematology		X				X
Biochemistry		X				X
Coagulation		X				
Urinalysis		X				X
Infectious serology		X				
HbA1c, fasting C-peptide		X				
Pregnancy test (females only)[5]		X	X			X
Drug screen		X				
Dosing visit exclusion/ withdrawal criteria			X	X[6]		
Randomization			X[4]			
IMP administration			X	X	X	
Missed meal bolus induced hyperglycemia				X		
Basal insulin suspension induced hyperglycemia					X	
Correction bolus (via pump)				X		
Correction bolus (via syringe)					X	
Blood sampling for insulin PK (see Tables 2 and 3)				X	X	

Trial Period	**Screening Period**		**Treatment Period 1 and 2**			**Follow-up**
Visit no.	**0**	**1**	**2 and 3**			**4**
	Informed Consent	**Screening**	**Induced hyperglycemia and recovery**			**Final examination**
Timing	≥ 1 day before Visit 1	1-28 days prior to Visit 2	3-14 days between Visit 2 and Visit 3			3-7 days after Visit 3
Day			Day -1	Day 1	Day 2	
In-house Visit/Period			X	X	X	
Blood sampling for plasma glucose PD and safety (see Tables 2 and 3)				X	X	
Blood sampling for ketones					X	
Adverse events		X	X	X	X	X
Concomitant medication		X	X	X	X	X
Pre-defined meals			X	X		

[1] Check that informed consent has been signed and dated
[2] Re-check of subject eligibility on Visit 2 Day -1 only.
[3] Weight only
[4] V2 only
[5] Pregnancy test in women will be performed according to Section 8.9.2
[6] Re-check of dosing visit exclusion criteria.

2.3 Assessment Schedules

Table 2 Assessment Schedule for Visits 2 and 3, Days -1 and 1

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other
Day -1 17:00		Subject arrives at the trial site and continued eligibility will be checked		X	Dosing visit exclusion criteria, AEs, concomitant medication, alcohol breath test, vital signs, ECG, physical examination, urine pregnancy test, weight[4]
17:30		Randomization (Visit 2 only) Discontinue subject's own insulin pump if not using Medtronic 640G; insert new infusion set; Start study insulin pump with IMP (subject's usual basal rate)			
18:00		Pre-defined evening meal Covered by individual meal bolus		X	
Day 1 04:00		START overnight stabilisation i.v. insulin glulisine or glucose infusion (if needed) Morning plasma glucose target (126 ± 20 mg/dL) ⬇		Sampling approx. every 30 min. or more frequently, if needed ⬇	
05:00		Fixed basal rate (single hourly rate) of CSII from at least -3 h until end of meal test (B + 5 h)			
07:30	-30 min	STOP i.v. insulin or glucose infusion (if any) Maintain PG at in the range of 126 ± 20 mg/dL			
Day 1 08:00	0	Standard liquid meal	X (pre-meal)	X (pre-meal)	Dosing visit exclusion criteria, AEs, concomitant medication
	15min	Liquid meal fully consumed		X	
	30min	Plasma glucose measurement: every 10 minutes if PG ≤ 200 mg/dL and every 5 minutes if PG > 200 mg/dL ⬇		X ⬇	
	B[2]	Confirmatory glucose measurement if PG > 240 mg/dL, followed by pump correction bolus	X[3]	X[3]	
	B + 5min		X	X	
	B + 10min		X	X	

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other
	B + 15min	As soon as PG ≤ 140 mg/dL is measured, a confirmatory PG is performed	X	X	
	B + 20min		X	X	
	B + 25min		X	X	
	B + 30min		X	X	
	B + 35min		X	X	
	B + 40min		X	X	
	B + 45min		X	X	
	B + 50min		X	X	
	B + 55min		X	X	
	B + 1h		X	X	
	B + 65min			X	
	B + 70min		X	X	
	B + 75min			X	
	B + 80min			X	
	B + 85min			X	
	B + 90min		X	X	
	B + 95min			X	
	B + 100min			X	
	B + 105min		X	X	
	B + 110min			X	
	B + 115min			X	
	B + 2h	If PG > 140 mg/dL, PG sampling will continue every 5 minutes If PG ≤ 140 mg/dL, PG sampling will be every 15 minutes	X	X	
	(B + 125 min)	If PG > 140 mg/dL		(X)	
	(B + 130min)	If PG > 140 mg/dL		(X)	
	B + 135min		X	X	
	(B + 140min)	If PG > 140 mg/dL		(X)	
	(B + 145min)	If PG > 140 mg/dL		(X)	
	B + 150min		X	X	
	(B + 155min)	If PG > 140 mg/dL		(X)	
	(B + 160min)	If PG > 140 mg/dL		(X)	
	B + 165min		X	X	
	(B + 170min)	If PG > 140 mg/dL		(X)	
	(B + 175min)	If PG > 140 mg/dL		(X)	
	B + 3h		X	X	
	(B + 185min)	If PG > 140 mg/dL		(X)	
	(B + 190min)	If PG > 140 mg/dL		(X)	
	B + 195min		X	X	
	(B + 200min)	If PG > 140 mg/dL		(X)	
	(B + 205min)	If PG > 140 mg/dL		(X)	
	B + 210min		X	X	
	(B + 215min)	If PG > 140 mg/dL		(X)	
	(B + 220min)	If PG > 140 mg/dL		(X)	
	B + 225min		X	X	
	B + 230min	If PG > 140 mg/dL		(X)	
	B + 235min	If PG > 140 mg/dL		(X)	
	B + 4h		X	X	
	(B + 245min)	If PG > 140 mg/dL		(X)	
	(B + 250min)	If PG > 140 mg/dL		(X)	

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other
	B + 255min		X	X	
	(B + 260min)	If PG > 140 mg/dL		(X)	
	(B + 265min)	If PG > 140 mg/dL		(X)	
	B + 270 min		X	X	
	(B + 275min)	If PG > 140 mg/dL		(X)	
	(B + 280min)	If PG > 140 mg/dL		(X)	
	B + 285min		X	X	
	(B + 290min)	If PG > 140 mg/dL		(X)	
	(B + 295min)	If PG > 140 mg/dL		(X)	
	B + 5h	End of experiment Resume of subject's usual basal rate	X	X	
13:30		Free-choice lunch meal Covered by individual meal bolus			
19:00		Pre-defined evening meal Covered by individual meal bolus			

[1] Plasma glucose will be analysed at the trial site using the CCI glucose analyser.

[2] B stands for time of bolus administration.

[3] Prior to bolus administration, two PK samples for PK insulin baseline determination will be taken.

[4] Only on Visit 2.

Table 3 Assessment Schedule Example for Visits 2 and 3, Day 2

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other[2]
0:00		Fixed basal rate (single hourly rate) of CSII from at least -3 h prior to basal insulin suspension			
02:00		START overnight stabilisation i.v. insulin glulisine or glucose infusion (if needed) Plasma glucose target 126 ± 20 mg/dL		Sampling approx. every 30 min. or more frequently, if needed	
	-30 min	STOP i.v. insulin or glucose infusion (if any) Maintain PG at in the range of 126 ± 20 mg/dL	X	X	
	-15 min		X	X	
04:00 to 06:00	0	Basal insulin suspension 8-10 hours after dinner meal on Day 1: Stop basal insulin rate Morning plasma glucose target (126 ± 20 mg/dL)	X	X	X
	15 min	Glucose measurement: every 15 minutes If PG ≤ 200 mg/dL and every 5 minutes If PG > 200 mg/dL Insulin PK measurement: every 15 min	X	X	Ketones, every 30 min
	B[3]	Confirmatory glucose measurement if PG > 240 mg/dL followed by IMP correction bolus with a syringe	X[4]	X	Ketones[5]
	B + 5min	As soon as PG ≤ 140 mg/dL is measured, a confirmatory PG is performed	X	X	
	B + 10min		X	X	
	B + 15min		X	X	
	B + 20min		X	X	
	B + 25min		X	X	
	B + 30min		X	X	Ketones
	B + 35min		X	X	
	B + 40min		X	X	
	B + 45min		X	X	
	B + 50min		X	X	
	B + 55min		X	X	
	B + 1h		X	X	Ketones
	B + 65min			X	
	B + 70min		X	X	
	B + 75min			X	
	B + 80min			X	
	B + 85min			X	
	B + 90min		X	X	Ketones
	B + 95min			X	
	B + 100min			X	

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other[2]
	B + 105min		X	X	
	B + 110min			X	
	B + 115min			X	
	B + 2h	If PG >180 mg/dL: Give additional correction bolus If PG > 140 mg/dL, PG sampling will continue every 5 minutes If PG ≤ 140 mg/dL, PG sampling will be every 15 minutes	X	X	Ketones
	(B + 125 min)	If PG > 140 mg/dL		(X)	
	(B + 130min)	If PG > 140 mg/dL		(X)	
	B + 135min		X	X	
	(B + 140min)	If PG > 140 mg/dL		(X)	
	(B + 145min)	If PG > 140 mg/dL		(X)	
	B + 150min		X	X	Ketones
	(B + 155min)	If PG > 140 mg/dL		(X)	
	(B + 160min)	If PG > 140 mg/dL		(X)	
	B + 165min		X	X	
	(B + 170min)	If PG > 140 mg/dL		(X)	
	(B + 175min)	If PG > 140 mg/dL		(X)	
	B + 3h		X	X	Ketones
	(B + 185min)	If PG > 140 mg/dL		(X)	
	(B + 190min)	If PG > 140 mg/dL		(X)	
	B + 195min		X	X	
	(B + 200min)	If PG > 140 mg/dL		(X)	
	(B + 205min)	If PG > 140 mg/dL		(X)	
	B + 210min		X	X	Ketones
	(B + 215min)	If PG > 140 mg/dL		(X)	
	(B + 220min)	If PG > 140 mg/dL		(X)	
	B + 225min		X	X	
	B + 230min	If PG > 140 mg/dL		(X)	
	B + 235min	If PG > 140 mg/dL		(X)	
	B + 4h		X	X	Ketones
	(B + 245min)	If PG > 140 mg/dL		(X)	
	(B + 250min)	If PG > 140 mg/dL		(X)	
	B + 255min		X	X	
	(B + 260min)	If PG > 140 mg/dL		(X)	
	(B + 265min)	If PG > 140 mg/dL		(X)	
	B + 270 min		X	X	Ketones
	(B + 275min)	If PG > 140 mg/dL		(X)	
	(B + 280min)	If PG > 140 mg/dL		(X)	
	B + 285min		X	X	
	(B + 290min)	If PG > 140 mg/dL		(X)	
	(B + 295min)	If PG > 140 mg/dL		(X)	
	B + 5h	End of experiment Subject resumes usual pump therapy with own insulin pump. Subject receives lunch	X	X	Ketones

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other[2]
16:00		Subject may leave the trial site or remain in unit overnight at the discretion of the Investigator			AEs, concomitant medication, vital signs, physical examination, glucose for safety

[1] Plasma glucose will be analysed at the trial site using the CCI glucose analyser.

[2] Blood sampling for PG measurment including threshold confirmation and PK assessment have priority and blood samples for ketone assessment should be taken thereafter.

[3] B stands for time of bolus administration.

[4] Prior to bolus administration, two PK samples for PK insulin baseline determination will be taken.

[5] A plasma sample for ketone concentration will be taken preferrably prior to the administration of the correction bolus but may be taken immediately thereafter in case of too many simoultaneous activities delaying the time of dosing.

3 INTRODUCTION

There is an unmet medical need for fast prandial insulin analogs with improved pharmacokinetic (PK) and glucodynamic (GD) characteristics.

LY900014 is an ultra-rapid-acting insulin lispro formulation that has shown an increased early absorption compared to commercially available insulin lispro (Humalog®; Eli Lilly). LY900014 aims to closely mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions and allow increased flexibility of the time of dosing relative to a meal.

This trial is intended to test this new formulation of insulin lispro (LY900014) in subjects with type 1 diabetes mellitus (T1DM) using continuous subcutaneous insulin infusion (CSII). The aim of the study is to compare the onset of insulin action following LY900014 administration in comparison to Humalog® on controlling hyperglycaemia, in a similar situation as when a subject experiences hyperglycaemia by forgetting to deliver a bolus after consuming a meal or when there is suspension of insulin delivery e.g. due to a malfunction of the insulin pump.

3.1 Background Information on Investigational Medicinal Products (IMPs)

3.1.1 Insulin lispro

The insulin analog insulin lispro (Humalog®) has been shown to be absorbed more quickly than regular human insulin (Humalog® package insert, 2015). In healthy volunteers given subcutaneous (SC) doses of insulin lispro ranging from 0.1 to 0.4 units (U)/kg, peak serum levels were seen 30 to 90 minutes after dosing (Humalog® package insert, 2015). However, the general consensus is that rapid-acting insulin is still not rapid enough to match carbohydrate absorption profiles, which limits efficacy and dosing flexibility. An ultra-rapid-acting prandial insulin would shift the PK/GD of insulin analogs so that they have an even faster onset to better match carbohydrate absorption and also allow greater flexibility in the time of dosing relative to meals.

3.1.2 ~~Insulin~~ LY900014

LY900014 represents a new formulation that contains insulin lispro, treprostinil, citrate and other excipients. This formulation involves the novel use of a microdose of treprostinil (CCI [redacted]) as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient to elicit a systemic effect. Treprostinil is a prostacyclin analogue, administered either through inhalation [redacted] C C I as an intravenous (IV) infusion or as a continuous SC administration for the treatment of symptomatic pulmonary arterial hypertension (PAH) and has been approved in the US since 2002 and in Germany since 2006 (AMIS database [WWW]). Sodium citrate, an excipient that speeds insulin absorption (at least in part by enhancing vascular permeability), is also included in the formulation to further enhance the absorption of insulin lispro. Each of the other excipients (such as magnesium chloride) in the LY900014 formulation is listed in the US Food and Drug Administration (FDA)'s Generally

Recognized as Safe Food Additives database and in the FDA's Inactive Ingredients in Approved Drugs database.

LY900014 has been evaluated in 19 completed Phase 1 studies and three Phase 3 clinical studies. Seven clinical pharmacology studies were conducted using a developmental formulation of LY900014 and 12 studies were conducted using the final formulation of LY900014. These included studies in 304 healthy subjects, 295 subjects with T1DM, and 103 subjects with T2DM administered at least 1 dose of LY900014. Two clinical pharmacology studies were conducted using CSII therapy in 54 subjects with T1D. In addition, a total of 1165 subjects with T1DM or T2DM received LY900014 in the Phase 3 studies.

Potential risks associated with LY900014, derived from the known risks of insulin lispro (Humalog®), are hypoglycaemia, hypersensitivity reactions (localized allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral edema (Humalog® package insert, 2015).

Notably, across all doses in the studies that have evaluated treprostinil[CCI] as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those AEs associated with systemic absorption of treprostinil, as described in the[CCI] package insert (2014). The exposures of treprostinil in LY900014 in this study are expected to be undetectable compared to those observed in the dose ranges previously explored with SC bolus administration of treprostinil and are expected to be substantially lower than those observed in the treatment of PAH. No known potential risks are associated with the microdose amount of treprostinil in the LY900014 formulation.

In preclinical safety pharmacology and toxicity studies, or clinical pharmacology studies involving LY900014 or treprostinil alone, other than known risks associated with Humalog® and [CCI], no additional risks were identified. Additionally, local and systemic toxicity profiles of Humalog® and[CCI] do not suggest the potential for additive or synergistic toxicity.

3.2 Rationale for the Trial

Patients with T1DM sometimes experience hyperglycaemic events, despite good glycaemic control, requiring immediate correction. An insulin analogue with a faster onset of action might benefit these patients by providing a faster transition to normoglycaemia.

The experimental setup of this study will simulate a situation in which a subject has to correct hyperglycaemia after a meal where prandial bolus was missed. Similarly, the study design will also simulate a situation in which subjects experience malfunction of the pump with suspension of insulin delivery and has to correct subsequent hyperglycaemia using an injected bolus of insulin.

4 OBJECTIVES AND ENDPOINTS

4.1 Objectives

This trial investigates the pharmacodynamic and pharmacokinetic responses of LY900014 and Humalog® (insulin lispro) in subjects with diabetes mellitus type 1 during the following situations:

4.1.1 Primary objective:

- To compare the time to recovery from hyperglycaemia following a missed meal bolus with LY900014 vs. Humalog®, given as a correction bolus via pump infusion
- To compare the time to recovery from hyperglycaemia following basal insulin suspension with LY900014 vs. Humalog®, given as a correction bolus via syringe injection

4.1.2 Secondary objectives:

- To compare the pharmacodynamic and insulin lispro pharmacokinetic following a correction bolus of LY900014 vs. Humalog® during recovery from hyperglycaemia following a missed meal bolus.
- To compare the pharmacodynamic and insulin lispro pharmacokinetic following a correction bolus of LY900014 vs. Humalog® during recovery from hyperglycaemia after basal insulin suspension.
- To assess the safety and tolerability of LY900014 and Humalog.

4.1.3 Exploratory objectives:

- To assess the blood glucose response after basal insulin suspension for LY900014 vs. Humalog®.

4.2 Endpoints

4.2.1 Primary endpoints:

- Time to recovery from hyperglycemia (time of correction bolus to time when PG = 140 mg/dL)

4.2.2 Secondary endpoints:

PD endpoints:

- $AUC_{(B\text{-}tPG140)}$, area under the PG curve but above 140 mg/dL from time of correction bolus (B) to time when PG is 140 mg/dL)
- $AUC_{(B\text{-}tPG180)}$, area under the PG curve but above 180 mg/dL from time of correction bolus (B) to time when PG is 180 mg/dL)
- Rate of change in PG (the change in PG at the time of bolus IMP administration to PG = 140 mg/dL measurement divided by the duration of time for this interval)
- PG_{max}, maximum observed plasma glucose

PK endpoint:

- t_{max}, time to maximum observed insulin concentration.
- Early 50% t_{max}, time to half-maximum before C_{max}.
- $AUC_{(0\text{-}15min)}$, are under the insulin curve from 0 to 15 minutes.
- $AUC_{(0\text{-}30min)}$, are under the insulin curve from 0 to 30 minutes.

4.2.3 Exploratory endpoints:

- Time to hyperglycaemia (PG > 240 mg/dL) after basal insulin suspension
- Peak ketone concentration after basal insulin suspension

4.2.4 Safety endpoints:

- Adverse Events

Further endpoints are defined in Section 13 and may be defined in the Statistical analysis plan (SAP).

5 TRIAL DESIGN

5.1 Type of Trial

Single center, randomized, two-treatment, subject- and investigator-blinded, 2-period cross-over trial in subjects with T1DM.

A schematic trial overview is given in Section 2, Figure 1.

5.2 Randomization

This is a randomized trial. Assignment to one of two treatment sequences (LY900014 followed by Humalog® or Humalog® followed by LY900014) will take place at the trial site.

The randomization list will be provided by Profil. A subject will only be randomized if he/she complies with all inclusion/exclusion and dosing visit exclusion criteria. Randomization should occur as close as possible to the first administration of IMP. When a subject is randomized in the trial, he/she must always be assigned to the lowest available randomization number available from the randomization list. Up to 28 subjects will be randomized to ensure that at least 24 can be evaluated.

Randomization numbers will be as follows:

- Randomization numbers starting with 101, 102, 103…
- Corresponding randomization numbers for replacements: 201, 202, 203…

Replacement subjects must always be assigned to the same sequence as the subject they replace (please see Section 6.6).

5.3 Blinding and Code Breaking Procedures

This is a subject- and investigator-blind randomized trial. The CRU personnel who will prepare the pump reservoirs for each treatment period and the syringe for correction bolus administration on Day 2 and administer the drug (only on Day 2, Day 1 administration can be done by blinded personnel) will not be blinded and will be separate and distinct from those who are involved in subject care. The sponsor including the Lilly CP/Lilly study team will be unblinded. Blinding will be maintained throughout the conduct of the study as described in a separate blinding document.

Treatment assignment will be kept strictly confidential and accessible only to authorized persons until after the time of un-blinding. Codes with treatment assignment will, however, be readily available to the blinded personnel in case of an emergency.

Two sets of sealed codes with the subject randomization number containing information about the treatment at each visit will be prepared for each subject. One set will be kept at the trial site in the office of the physician on duty (during the entire trial period), the other set will be kept under the responsibility of the Sponsor and are to be used in case of code break need.

The code for a particular subject may be broken by an investigator in case of a medical emergency if knowing the identity of the treatment allocation could influence the treatment of the subject. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents and on the code envelope. The breaking of blinded codes in case of medical emergency for one subject should not unblind the trial personnel to the treatment information of other subjects. The person performing the unblinding should inform as few people as possible about the result of the unblinding. All persons unblinded for a specific subject should be documented.

If the trial site needs to break the code, the Sponsor should, if possible, be contacted prior to breaking the code. In all cases, the monitor must be notified within 24 hours after the code has been broken.

All codes (whether broken or not) must be kept throughout the trial period. The codes kept at the trial site will be checked by the monitor and the close-out visit report should confirm adequate documentation of any code breaks (if applicable).

5.4 Investigational Treatment of Subjects

Each subject will be randomly allocated to a sequence of the 2 treament periods with administration of LY900014 and Humalog®, respectively. During the Treatment Periods, study drug will be administered with a Medtronic MiniMed 640G pump and with an insulin syringe.

A standardized infusion set (catheter with standard cannula length and tubing) will be inserted into the abdominal wall on Day –1 of each treatment period, which should stay at the same catheter insertion-site location for the complete duration of the experiments during the treatment period. In case of a pump occlusion alarm prior to the experimental procedures on Day 1 and Day 2 (i.e. after catheter insertion on Day -1 or during the night of Day 2), the infusion set including the catheter can be changed until 3:00 of Day 1 and Day 2. If a catheter needs to be changed due to a pump malfunction or occlusion alarm during the experimental procedures, the subject may repeat the respective study day once only if the maximum blood loss over the entire study (that is, the blood loss during the past study days/period and the expected blood loss of upcoming study days/period) will not exceed approximately 500 mL.

Subjects will continue their individual CSII basal rate using the insulin pump during the experiments/treatment periods. However, during the meal test procedure on Day 1 and the basal insulin suspension procedure on Day 2, the basal rate will be changed to a single hourly rate based on the subject's mean basal needs from at least 3 hours before the start of meal ingestion (Day 1) or basal insulin suspension (Day 2). On Day 1, the basal rate will remain as a single hour

rate 5 hours after bolus administration. On Day 2, the basal rate will be suspended until 5 hours after the correction bolus administration. After termination of the respective experimental procedure on trial Days 1 and 2, the basal rate will be changed back to the subjects individual basal rate.

A bolus dose of insulin lispro (LY900014 or Humalog®) will be individualized per subject to correct hyperglycaemia induced by the carbohydrate content of the liquid meal on Day 1 and to correct hyperglycaemia due to suspension of insulin delivery by the pump. The bolus will be administered by means of the pump on Day 1 using a rapid single wave bolus (administration speed = 15 U/min). and by means of an insulin syringe on Day 2. The individualized bolus dose on Day 1 will be a joint decision of the subject and the investigator based on the subjects usual prandial needs to cover the nutritional content of the liquid meal. The correction bolus dose on Day 2 will be 0.2 U/kg body weight. Bolus doses will be administered when glycaemia level is 240 mg/dL or above and confirmed by a second CCI measurement.

The correction bolus doses of LY900014 and Humalog on the experimental days should in general be identical between treatment periods. However, the bolus dose of an experimental day can be subjected to changes when more information is gathered during the execution of the study, for example in case the initially planned boli are not sufficient to control hyperglycaemia or when the boli induce hypoglycaemia in a great proportion of subjects.

5.5 Duration

Planned date for First subject first visit (FSFV): February 2020

Planned date for Last subject last visit (LSLV): June 2020

FSFV is defined as the first informed consent obtained in this trial.

LSLV is defined as the last scheduled trial visit as detailed in Section 2.1.

The end of the clinical trial is defined as LSLV.

Actual time-lines may vary.

The total trial duration for a subject will be about 2 to 9 weeks.

5.6 Stopping Rules

No specific stopping rules in addition to Sections 6.5 and 14.4 are applicable for this trial.

5.7 Rationale for the Trial Design and Treatment

A crossover design is chosen in order to reduce variability as each subject acts as its own control. The total number of subjects needed with a crossover design is decreased as compared to a parallel group design.

Randomization and blinding is used in order to avoid bias introduced through an association between allocation order of IMP and subject characteristics.

Bolus doses administered during the meal test and basal insulin suspension procedure will be individualized based on individual requirements, to ensure robust and comparable PD responses after hyperglycemia induction and safety of the subjects. The bolus dose for the meal test will be based on the individual postprandial bolus of the subjects, which is believed to be sufficient to control hyperglycemia induced by the meal. In the case of the basal insulin suspension procedure, the bolus dose is based on literature, in which a large bolus dose is needed to overcome possible insulin resistance (1, 2). To enable an evaluation of the insulin lispro PK and PD responses, the individual doses will be kept identical within each subject during both treatment periods (LY900014 and Humalog), and conditions during the experimental days will be standardized regarding meal composition, CSII basal rate and fasting conditions.

A minimum 3-day resting period between the 2 dosing visits (Visits 2 and 3) is introduced to ensure a sufficient wash-out period from previous dosing to avoid any carry-over effect.

6 TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1 Number of Subjects to be Studied

Planned number of subjects to be randomized: Up to 28 subjects to ensure 24 evaluable subjects

Expected number of subjects to complete the trial: 24

6.2 Inclusion Criteria

1. Signed and dated informed consent obtained before any trial-related activities. Trial-related activities are any procedures that would not have been done during normal management of the subject.
2. Male or female subject with diabetes mellitus type 1.
3. Age between 18 and 64 years, both inclusive.
4. Body Mass Index (BMI) between 18.5 and 30.0 kg/m^2, both inclusive.
5. HbA1c <= 8.5%.
6. Fasting negative C-peptide (<= 0.30 nmol/L).
7. Total insulin dose of < 1.2 (I)U/kg/day.
8. Diabetes duration of at least 12 months.
9. Using CSII and a stable insulin regimen for at least 3 months prior to inclusion into the trial.
10. Willingness to comply with study procedures including consumption of the test meal.
11. Considered generally healthy (apart from diabetes mellitus type 1) upon completion of medical history and screening safety assessments, as judged by the Investigator.
12. Have venous access sufficient to allow cannulation for blood sampling as required by the protocol.

6.3 Exclusion Criteria

1. Known or suspected hypersensitivity to insulin lispro or any of the excipients or to any component of the IMP formulation.
2. Previous participation in this trial. Participation is defined as randomized.
3. Receipt of any medicinal product in clinical development within 30 days or at least 5 half-lives of the related substances and their metabolites (whichever is longer) before randomization in this trial.

4. Currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
5. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction.
6. Any history or presence of cancer except non-metastatic basal cell skin cancer or squamous cell skin cancer as judged by the Investigator.
7. Any history or presence of clinically relevant comorbidity (with the exception of conditions associated with diabetes mellitus), as judged by the investigator
8. Signs of acute illness as judged by the Investigator.
9. Any serious systemic infectious disease during four weeks prior to first dosing of the trial drug, as judged by the Investigator.
10. Known slowing of gastric emptying and or gastrointestinal surgery that, in the opinion of the investigator, might change gastrointestinal motility and food absorption.
11. Clinically significant abnormal values for haematology, biochemistry, coagulation, or urinalysis as judged by the Investigator.
12. Systolic blood pressure < 100 mmHg or >139 mmHg and/or diastolic blood pressure < 60 mmHg or > 89 mmHg (one repeat test will be acceptable in case of suspected white-coat hypertension).
13. Heart rate at rest outside the range of 50-90 beats per minute.
14. Clinically significant abnormal standard 12-lead electrocardiogram (ECG) after 5 minutes resting in supine position at screening.
15. Widespread subcutaneous lipodystrophy in the abdomen.
16. Proliferative retinopathy or maculopathy as judged by the Investigator based on a recent (<1.5 years) ophthalmologic examination.
17. Severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator.
18. More than one episode of severe hypoglycaemia with seizure, coma or requiring assistance of another person during the past 6 months.
19. Hospitalisation for diabetic ketoacidosis during the previous 6 months.
20. Current use of any glucose-lowering agents other than insulin within 3 months prior to screening.
21. Significant history of alcoholism or drug abuse as judged by the Investigator or consuming more than 24 grams alcohol/day (for males), 12 grams alcohol/day (for females) on average.
22. A positive result in the alcohol and/or urine drug screen at the screening visit.
23. Smoking more than 5 cigarettes or the equivalent per day.

24. Inability or unwillingness to refrain from smoking and use of nicotine substitute products one day before and during the inpatient period.
25. Tested positive for Hepatitis Bs antigen.
26. Tested positive for hepatitis C antibodies. (Presence of hepatitis C antibodies will not lead to exclusion if liver function tests are normal and a hepatitis C polymerase chain reaction is negative).
27. Positive result to the test for HIV-1/2 antibodies or HIV-1 antigen.
28. Any (prescription and non-prescription) medication within 14 days before first IMP administration, other than acceptable concomitant medication as judged by the investigator.
29. Receiving chronic (lasting longer than 14 consecutive days), systemic, or inhaled glucocorticoid therapy (excluding topical, intra-articular, and intraocular preparations); or have received such therapy within the 4 weeks before screening .
30. Blood donation or blood loss of more than 500 mL within the last month.
31. Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation.
32. If female, pregnancy or breast-feeding
33. Women of childbearing potential who are not using a highly effective contraceptive method
34. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

    Explanatory note on Exclusion Criterion 33: A woman is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile due to hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

    Explanatory note on Exclusion Criterion 33: Highly effective contraceptive methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include:

    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - vasectomized partner, provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success (absence of sperm).

- sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

6.4 Dosing Visit Exclusion Criteria

Subjects who fulfil one or more dosing visit exclusion criteria (see below) before start of the meal test procedure (on Day-1 of treatment period 1 or 2, respectively) will be excluded from the trial day. The trial day (and subsequently treatment period) may be rescheduled 1-14 days later. Each of the treatment periods can only be rescheduled once. A treatment period may not be re-scheduled once the first meal test has begun.

1. Consumption of alcohol within 24 hours prior to each treatment period, or a positive result of the breath alcohol test.Consumption of coffee, tea, chocolate, cola, energy drinks and/or energy drinks containing methylxanthine within 8 hours to each treatment period.

2. Strenuous exercise within the last 48 hours prior to each treatment period.

3. Any medical condition or AE that could interfere with glucose metabolism, as judged by the Investigator.

4. Any use of prescription or non-prescription medication according to exclusion criterion no. 20, 28 or 29.

5. Fasting for less than 10 hours before start of meal test procedure on Day 1.

6. Hypoglycaemia (plasma glucose <70 mg/dL) posing a safety problem (as judged by the Investigator) within 24 hours prior to first meal test of each treatment period.

7. Injection of a bolus of more than 6 U of a fast-acting insulin analog between 7 and 12 hours before dosing.

6.5 Discontinuation Criteria

A subject has the right to withdraw from the trial at any time for any reason. A subject's trial participation will also be discontinued for the following reasons:

1. At the discretion of the Investigator if judged non-compliant with trial procedures.

2. At the discretion of the Investigator due to safety concerns.

3. Due to a protocol violation, which, in the clinical judgement of the Investigator or after discussion with the Sponsor, may invalidate the trial by interfering with the PK and PD response of IMP.

4. Due to a concurrent illness, which, in the clinical judgement of the Investigator or after discussion with the Sponsor, may invalidate the trial by interfering with the PK and PD response of IMP.

5. Adverse event (AE): Subject reports symptoms, which are considered unacceptable by the Investigator.

6. If a subject experiences severe hypoglycaemia (according to Section 9.4) at any time during the study

7. Pregnancy or intention to become pregnant.

8. Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

9. Participation in the study needs to be stopped for regulatory or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

In case of discontinuation following dosing with one of the IMPs the subject will, if possible, be called in for a complete follow-up visit. The date and reason of discontinuation will be entered into the CRF. Four categories of discontinuation are distinguished:

a) Withdrawal by subject. The reason stated by the subject for discontinuation should be stated

b) Protocol-specific discontinuation criterion is met (from list above)

c) Lost to follow-up: cessation of participation without notice or action by the subject

d) Trial terminated by Sponsor

e) Death

f) Other

The end of trial form will be completed for all prematurely discontinued subjects.

6.5.1 Hepatic Criteria for Discontinuation

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT (alanine aminotransferase) AST (aspartate aminotransferase) >8X ULN (upper limit of normal)
- ALT or AST >5X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or INR >1.5 or

- ALT or AST >3X ULN the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP (alkaline phosphatase) >3X ULN
- ALP>2.5X ULN and TBL >2X ULN
- ALP>2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.6 Subject Replacement

A total of 24 subjects should complete the trial according to the sample size calculation (see Section 13.1). To account for discontinued subjects (defined as subjects concluding participation, prior to completion of all protocol-required elements after enrollment/randomisation), up to 28 subjects will be randomised. In case of more than 4 discontinued subjects, four additional replacement subjects may be enrolled (maximum total number of enrolled subjects will not exceed 32 subjects). A replacement subject will be assigned to the same treatment sequence as the subject being replaced.

6.7 Rationale for Trial Population

The planned population for the trial will be subjects with type 1 diabetes which are an important target population for treatment with LY900014. Restricting the population to subjects on CSII will facilitate study procedures, as it will enable switching to the study treatment with a minimised risk for subjects safety.

The inclusion and exclusion criteria will limit the trial population to subjects being in good health, which should help minimize safety risks for the subjects and which should also reduce variability of pharmacokinetic and pharmacodynamic response. However, the results from this trial are still considered to be generally applicable to all patients with type 1 diabetes using CSII treatment.

7 TRIAL MATERIALS

7.1 Investigational Medicinal Products (IMPs)

The IMPs listed in Table 4 will be used in this trial:

Table 4: Specification of Investigational medicinal products (IMPs) used in the trial

IMPs	Strength	Pharmaceutical dosage form	Dose per administration	Route of administration
LY900014	100 U/mL	Solution for injection filled in 3.0 mL pump reservoir/10mL vial	Basal and bolus infusion based on individual needs	subcutaneous infusion via CSII/injection via syringe
Humalog® (insulin lispro)	100 U/mL	Solution for injection filled in 3.0 mL pump reservoir/10mL vial	Basal and bolus infusion based on individual needs	subcutaneous infusion via CSII/injection via syringe

Manufacturer of LY900014 is Eli Lilly and Company and will be provided by Eli Lilly.

Manufacturer of Humalog® is Eli Lilly and Company and will be provided by Eli Lilly.

IMPs will be administered subcutaneously in the abdomen by use of:

- an insulin pump (Medtronic MiniMed 640G) and Quick Set® (Medtronic, Meerbusch, Germany) infusion sets.
- an insulin syringe

For further information please refer to the Investigators Brochure (IB) of LY900014 and to the Summary of Product Characteristics (SmPC) of Humalog®.

7.2 Packaging and Labelling of Investigational Medicinal Product

Labelling of the IMPs will be in accordance with local regulations, trial requirements and Annex 13 (3).

Enough investigational medicinal products will be packed for the scheduled number of subjects. A buffer volume of IMPs will be provided in case of replacement of discontinued subjects or damaged IMPs.

7.2.1 Storage and Drug Accountability of Investigational Medicinal Product

All IMPs will be stored and handled in accordance with the manufacturer instructions and/ or the product labelling at the Investigator's site, e.g. for storage refrigerated (+2°C to +8°C) and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used, partly used and unused IMP/packaging must be kept by the Investigator and stored between +2°C and +8°C/at room temperature. Used and unused vials must be stored separately.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. Temperature of the refrigerator used for drug storage is monitored continuously, an alarm system is established. The Investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g. outside temperature storage). IMP that has been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use. The Investigator must take appropriate action to ensure correct storage.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each subject in a Drug Accountability Record. Storage locations, batch numbers and expiry dates are also documented in this form.

The drug accountability has to be performed in a timely manner.

7.2.2 Dispensing and Return of Investigational Medicinal Products

No IMPs may be dispensed to any person not enrolled in the trial.

Upon completion of the trial, the Sponsor will be responsible for destruction or storage of IMPs (used, partially used or unused). These duties can be delegated to the site and must be documented in the trial investigator file (TIF).

7.3 Retention Samples

No retention samples will be stored for this trial.

7.4 Preparation and Application of IMP

IMP administration will be in accordance with the randomization list provided by Profil.

An unblinded pharmacist at the site will fill the pump reservoirs and prepare the syringes for injection and attribute them to the respective subjects as per randomization schedule.

Non-investigational medicinal product (NIMP) used in this trial will be sourced from the German market and used from its original packaging.

8 VISITS AND ASSESSMENTS

8.1 Visit Procedures

Please refer to the information given in Section 2 for a general overview of the trial visits and the visit assessments and procedures. The following sections describe details of the visit assessments and procedures.

The Investigator must keep a subject screening and identification log.

8.2 Visit 0 – Informed Consent Visit

Prior to any trial-related activities, potential subjects will be provided with oral and written information about the trial course, the employed investigational products and the visit procedures. The subjects will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They have the opportunity to discuss all open questions and will have ample time to consider participation. Subjects who wish to participate in the trial will be asked to personally date and sign an informed consent form prior to any trial-related activities. Trial-related activities are any procedures that would not have been performed during normal management of the subject (including e.g. fasting for screening). Likewise, the Investigator must also personally date and sign the informed consent form prior to any trial related activities. All subjects will be provided with a copy of their own signed and dated informed consent form.

8.3 Visit 1 – Screening Visit

A rescheduling of the screening visit (within 1–7 days) is allowed once in case subjects have failed to be fasting.

Subjects will receive a screening number in ascending order starting with 001.

Subjects are screening failures if they are excluded from further trial participation after the screening visit before randomization.

Possible reasons for screening failure are failure to comply with all inclusion and exclusion criteria or withdrawal of eligible subjects after the screening visit by decision of the subject or the investigator.

Screened subjects who do not meet or comply with all inclusion and exclusion criteria are excluded (screening failures), and their data will be recorded on a screening failure form. The reason for exclusion must be recorded on the screening failure form. Detailed information about which data will be entered into the trial database will be described in the trial specific data management plan.

Re-screening of screening failures is generally not allowed according to Profil's Standard operating procedures (SOPs). Re-assessment of laboratory parameters will be allowed once if

handling issues, damaged samples, or haemolysed samples may have confounded the measurement results.

Eligible or potentially eligible subjects (lab results pending) will be provided with a Subject Identification Card (ID card), stating that the subject is participating in the trial and whom to contact (site address, Investigator name and telephone number). The subjects should be instructed to return the ID card to the Investigator at the last visit or to destroy the card after the last visit.

The subjects are reminded of their next visit to the trial site and are instructed to comply with the dosing visit criteria (Section 6.4) for this visit.

Before leaving the clinic, subjects are offered to consume a breakfast at the site.

8.4 Visit 2 and 3 – Dosing Visits

Please refer to the assessment schedule in Section 2.3 for the procedures and timing of assessments at the dosing visits. Please refer to the later sections in this chapter for a description of the assessments.

Results from the screening visit must be available at Visit 2 Day -1 and assessed to be acceptable by the Investigator. These results must be verified by the signing and dating of test results by the Investigator. The Investigator should document if out of range results are clinically significant.

At Visit 2 Day -1, subjects that comply with all the criteria for continuation in the trial (see Section 6.4 and 6.5) will be randomized (see Section 5.2) and continue with the visit procedures. Randomization should occur as close as possible to the first administration of IMP.

Day -1 to Day 1 – Missed meal bolus procedure

Subjects will attend the trial site in the afternoon of Day -1 at approximately 17:00.

Subjects' infusion set and reservoir of the insulin pump will be changed at the trial site and filled with either LY900014 or Humalog® according to the randomization list. Subjects who are not using a Medtronic 640G insulin pump will be provided with a Medtronic 640G insulin pump and will be trained in its use. Users of this pump may use their own pump for the experimental procedures. The pump will be used for IMP administration during the respective treatment periods. Except where otherwise noted, subjects will continue their individual basal rate and bolus regimen unless safety issues arise.

After catheter insertion a priming bolus of 1 U will be infused via CSII to ensure correct functioning of the pump.

Subjects will be served a pre-defined evening meal and will cover the meal with a bolus dose of the IMP according to his/her individual insulin needs.

Overnight, the basal insulin infusion rate will be maintained and a target fasting plasma glucose level in the range of 126 ± 20 mg/dL will be aimed for (see Section 8.8.1). In case of a pump

malfunction or infusion set occlusion overnight an additional infusion set change may be performed until 3:00 in the morning of Day 1.

In the morning of Day 1, a single hourly basal rate will be started from at least – 3 hours prior to meal ingestion. From approx. 08:00 , subject will undergo a meal test procedure with missed meal bolus to induce hyperglycaemia which will be followed by the administration of a correction bolus via the pump as described in Section 8.8.1. CCI [redacted] Before the start of the meal test procedure on Day 1, the dosing visit exclusion criteria (see Section 6.4) will be re-checked.

Blood samples for pharmacokinetic and pharmacodynamic assessments will be taken as detailed in Section 2.3. After the last blood sample has been taken and all meal test related procedures have been completed, the patient will be served a free-choice lunch meal as detailed in Section 8.10.

Day 1 to Day 2 – Basal insulin suspension procedure

In the evening of Day 1, subjects will be served a pre-defined evening meal and will cover the meal with a bolus dose of the IMP according to his/her individual insulin needs. After administration of this bolus dose no additional correction bolus should be administered subcutaneously.

Overnight, the basal insulin infusion rate will be fixed to a single hourly rate from at least – 3 hours prior to basal insulin suspension and a target fasting plasma glucose level in the range of 126 ± 20 mg/dL will be aimed for (see Section 8.8.1). In case of a pump malfunction or infusion set occlusion overnight an additional infusion set change may be performed until 3:00 in the morning of Day 2.

During the night of Day 2, subjects will have their basal insulin rate suspended to induce hyperglycaemia followed by the administration of a correction bolus via syringe as described in Section 8.8.3.

Blood samples for pharmacokinetic and pharmacodynamic assessments as well as for blood ketones will be taken as detailed in Section 2.3.

After completion of the basal insulin suspension procedure, the subject will be switched back to his/her usual CSII therapy and will be served a free-choice meal.

To ensure subjects safety and safe recovery from induced hyperglycaemia, the subject should stay at the trial site until his/her plasma glucose value have normalized, if deemed necessary by the Investigator.

However, at the discretion of the Investigator or per request by the subject, the subject may stay at the trial site for a longer period.

Before leaving the trial site, the subject must be informed about the symptoms of hypoglycaemia and about appropriate methods to treat hypoglycaemia. The appointment for the final examination will be confirmed with the subject.

8.5 Visit 4 – Follow-up Visit

A rescheduling of the follow-up visit (within 1–7 days) is allowed once in case subjects have failed to be fasting. If the subject has failed to be fasting at the rescheduled follow-up visit, the visit will be conducted in any case.

8.6 Assessment of Treatment Compliance

Trained members of staff will perform all administrations of the IMP during the meal test procedure on Day 1 and the pump interruption procedure on Day 2 at the trial site. The administered doses will be recorded in the Drug Accountability Form / CRF.

Pharmacokinetic assessments will support the surveillance of compliance with IMP administration.

8.7 Assessments for Pharmacokinetics

Blood samples for pharmacokinetic assessment of the IMP will be taken at specified time points, see Section 2.3.

A description of the sample handling and sample processing at the site will be included in the laboratory manual.

IMP concentrations will be measured by the special laboratory (see Names and Addresses for contact details). Validation documentation for the pharmacokinetic analysis must be available prior to sample analysis. Furthermore, a Bioanalytical Report will be prepared.

On Day 1 of each treatment period, the pharmacokinetic response following administration of the IMP as a correction bolus given by the insulin pump to treat hyperglycemia induced by ingestion of a meal will be assessed as described in Section 8.4.

On Day 2 of each treatment period, the pharmacokinetic response following administration of the IMP as a correction bolus given by a syringe to treat hyperglycemia after suspension of basal insulin delivery by the insulin pump will be assessed as described in Section 8.4.

8.8 Assessments for Pharmacodynamics

On Day 1 of each treatment period, hyperglycaemia will be induced by ingestion of a liquid meal without respective bolus administration. After reaching hyperglycaemia, the pharmacodynamic response after administration of an IMP correction bolus via the insulin pump will be assessed.

On Day 2 of each treatment period, the pharmacodynamic response after suspension of insulin delivery by the insulin pump will be assessed as well as after administration of a correction bolus via syringe as described in Section 8.4.

Plasma glucose will be analysed at the trial site using the CCI glucose analyzer PPD at the specified time intervals prior to and specified time points after IMP bolus administration according to Section 2.3.

8.8.1 Run-in and other experimental procedures on Day 1 and Day 2

Invasive procedures

Two intravenous cannulas (catheters) will be inserted: One cannula will be inserted in a vein of a forearm for sampling for serial PK and PD measurements. This cannula will be kept open by use of a mandrin/stylet. For controlled variable infusion of glucose or insulin glulisine (Apidra®) during the run-in period, a forearm vein of the contralateral arm will be cannulated with an adequate polytetrafluoroethylene (PTFE) catheter.

Run-in procedures

The run-in period will start during the night prior to the correction bolus administration of IMP on Day 1 and prior to basal insulin suspension on Day 2, at the preferred times described in Section 2.3 (i.e. at preferrably 4:00 hours on Day 1 and 2:00 hours on Day 2) or earlier if deemed necessary by the Investigator. Subjects should stay fasted after intake of the dinner meal on Day -1 and Day 1 until the end of the experimental procedures on the following day.

A variable i.v. infusion of insulin glulisine (15 U Apidra® [100 U/mL] in 49 mL saline and 1 mL of subject's blood) or glucose (20%, diluted with saline prior to infusion) will be initiated in order to obtain a plasma glucose target range of 126 ± 20 mg/dL. The insulin infusion rate and glucose infusion rate (GIR) will be recorded. Any insulin glulisine infusion should be stopped from 30 minutes prior to meal ingestion/basal insulin suspension, any glucose infusion should be stopped from 30 minutes prior to meal ingestion/basal insulin suspension.

The PG must be kept within a range of 126 ± 20 mg/dL the last 30 min prior to start of meal intakte. The PG level must not exceed each target range for more than 5 min, otherwise the run-in period should be adequately extended in order to fulfil the target ranges. Start of meal intake on Day 1 should start between 8:00 to 10:00 hours (8:00 preferred). Basal insulin suspension on Day 2 should start approx. 8-10 hours after the dinner meal on Day 1. The PG level prior to the start of the meal test and basal insulin suspension procedure during treatment period 2 should be similar to that of treatment period 1, if feasible.

Procedures in case of hypoglycaemia and hyperglycaemia during missed meal bolus and basal insulin suspension procedures

In case subject's plasma glucose concentration falls below 54 mg/dL (3.0 mmol/L, level 2 hypoglycaemia), the subject must be treated with either oral administration of rapidly absorbable carbohydrates or i.v. glucose as judged by the investigator to stop the hypoglycaemic episode

and the experimental procedure will be terminated. Date and time of termination (i.e., the start time of any treatment given for this hypoglycaemic episode) will be documented in the CRF. Hypoglycaemia with plasma glucose concentrations below 70 mg/dL (level 1) should not be treated until the completion of the meal test unless hypoglycaemic related symptoms are unacceptable for the subject.

In case subject's plasma glucose concentration rises above 306 mg/dL for more than 1 hour after correction bolus administration, or if the investigator deems it necessary, the subject will be treated with an additional bolus of the IMP (subcutaneously) at discretion of the investigator. The time of administration and amount of additional bolus will be documented in the CRF.

In both cases, blood samples for PK analysis will still be taken as planned.

8.8.2 Meal test procedure with missed meal bolus

Meal test period

A fixed composition meal will be served as liquid meal and should be consumed completely by the subject within 15 minutes after IMP administration. Ingestion of the meal will start after PG stabilisation and is defined as time point 0 (zero). No insulin bolus will be administered at this time point with the aim to induce postprandial hyperglycemia (PG > 240 mg/dL).

On Day 1, a liquid meal was chosen to rapidly increase plasma glucose concentration. The composition of the liquid meal is: 55% of carbohydrates, 15% protein and 30% fat. The liquid meal CCI [redacted] provides 63g of carbohydrates. The meals will be consistent for both treatment periods and for all individual subjects. However, adaptations in the planned amounts can be done for an individual subject when experience is gathered during the experimental procedures.

After completion of liquid meal intake, the subject should refrain from eating until the end of the meal test. Water consumption is not allowed during the first 2 hours after meal intake. Subjects will be required to consume the complete meal within the given time frame. In case the subject is not able to complete the meal on a meal test day, left-overs have to be weighed and respective non-consumed carbohydrates calculated and documented in the CRF. If a subject consumes less than the planned amount of the meal on the first treatment period the amount will be identical on the second treatment period. If this happens during the second treatment period the non-consumed amount will be weighted and documented.

Plasma glucose will be monitored until PG > 240 mg/dL has been measured and the result has been confirmed by a second measurement. At this time point (time point B0 (B zero)) the subjects individual bolus dose to cover the meal will be administered via the insulin pump. Blood samples for PK and PD assessments will be taken for the follwing 5 hours (see Section 2.3, Table 2).

In case subjects plasma glucose will not reach the PG >240 mg/dL, the meal test procedure will be aborted and repeated within 1-14 days. The subject will stay inhouse to proceed with trial

procedures until the end of the treatment period and an appointment for the repetition of the meal test procedure will be made, if feasible.

Subjects will be asked to lie in a semi-supine position after meal intake until 2 hours after IMP administration and in a supine or semi-supine position thereafter until the last blood sample for PK and PD has been taken. During the intake of the mixed meal the subjects will be allowed to sit.

After the end of the meal test procedure, the subject will continue with trial procedures as described in Section 8.4.

8.8.3 Basal insulin suspension procedure (Day 2)

Basal insulin suspension will start at any time between 8 and 10 hours after the dinner meal on Day 1 (e.g. between 4:00 and 6:00). Once plasma glucose will be in the target range, the basal rate will be set to zero (temporary basal rate of 0%) to suspended insulin delivery. Plasma glucose will be monitored regularly to follow the rise in plasma glucose concentration above 240 mg/dL and blood samples for PK analysis will be taken to analyse the decline in circulating insulin levelsaccording to Section 2.3 Table 3. As soon as a glucose measurement above 240 mg/dL has been measured and the result has been confirmed by a second measurement. Thereafter, a correction bolus of 0.2 U/kg body weight of the IMP will be administered via a subcutaneous injection in the periumbilical region using an insulin syringe. In addition, a plasma sample for ketone concentration will be taken during this time. During the following 5 hours blood samples for pharmacokinetic and pharmacodynamic assessments as well as for determination of blood ketones will be taken according to Section 2.3, Table 3.

The subject should stay in bed during the basal insulin suspension procedure and will not be allowed to consume anything except for water until the last blood sample for pharmacokinetic and pharmacodynamic assessment has been taken.

After the end of the basal insulin suspension procedure, the subject will resume their usual insulin treatment with their own pumps and continue with trial procedures as described in Section 8.4.

8.9 Assessments for Safety

8.9.1 Clinical Assessments

Adverse events

Adverse events (AEs) will be recorded in accordance with the procedures described in Section 9. Any clinically significant worsening of a previous finding must be reported as an AE.

During each contact with the trial site staff (site visits and telephone contacts) the subject must be asked about changes of their health status. This must be documented in the subject's medical record.

Concomitant illness and medical history

A concomitant illness is any illness that is present at the start of the trial (i.e. after signing the informed consent).

Medical history is an account of medical events that the subject has experienced in the past.

- Concomitant illnesses present at the start of the trial will be recorded in the CRF at screening.
- Relevant medical conditions/illnesses in the past will be recorded in the CRF at screening.

The information collected for concomitant illness and medical history should include diagnosis, date of onset, date of resolution or continuation.

Any change to a concomitant illness should be recorded during the trial, including end date, if applicable. A clinically significant worsening of a concomitant illness must be reported according to Section 9.

Physical examination

An examination of the following body systems will be performed:

- Head, ears, eyes, nose, throat (HEENT), incl. thyroid gland
- Heart, lung, chest
- Abdomen
- Skin and mucosae
- Musculoskeletal system
- Nervous system
- Lymph node
- Other findings

At the screening visit, any abnormality will be recorded and described in the CRF including the Investigator's assessment of clinical significance ('abnormal, not clinically significant' or 'abnormal, clinically significant'). Clinically significant findings at the screening visit should be recorded as concomitant illness.

At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant findings will be recorded as AEs.

Vital signs

An examination of the following vital signs will be performed:

- Diastolic and systolic blood pressure (mmHg) are measured after at least 5 min rest in a supine position. At the screening visit blood pressure is measured in both arms. The blood pressure from the arm with the higher systolic value is transcribed into the CRF and this arm is used for all subsequent measurements of the subject's blood pressure in this trial.
- Pulse (beats per min) measured after at least 5 min rest in a supine position.
- Body temperature, tympanic (ºC).
- Respiratory frequency.

In addition to the pre-specified assessments in Sections 2.2 and 2.3, blood pressure and pulse may be assessed at any time during the trial at the discretion of the Investigator. Additional measurements will not be recorded in the CRF.

Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed.

ECG parameters (Heart rate, PQ, QRS, QT, QTcB) and any abnormality will be recorded and described in the CRF including the Investigator's assessment of clinical significance ('abnormal, not clinically significant' or 'abnormal, clinically significant'). Clinically significant findings at at the screening visit should be recorded as concomitant illness.

Mean result (as reported by the ECG device) will be reported as heart rate. Aggregate data will be reported for all intervals. PQ will be reported as PR.

At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant findings will be recorded as AEs.

Plasma glucose for safety

During the trial, plasma glucose levels will be monitored at the trial site by a laboratory method (CCI Glucose Analyzer; PPD for safety and for pharmacodynamic assessments on Day 1 and Day 2. At the discretion of the Investigator additional plasma glucose measurements for safety may be made when there is a suspicion of a hypoglycaemic or hyperglycaemic episode. Plasma glucose measurements for safety should only be recorded in the CRF in case they are related to a hypoglycaemic episode. Hyperglycaemic episodes will not be recorded in the CRF unless these are assessed as severe adverse events by the investigator.

- In case of symptomatic Level 1 hypoglycaemic event (see Section 9.4) or in case of any Level 2 hypoglycemic event (see Section 9.4) outside the meal test and basal insulin suspension procedure (see Section 8.8.1 for respective treatement), the subject must be treated to alleviate the hypoglycaemic symptoms and/or to normalise plasma glucose ≥ 70 mg/dL. Rapid absorbable carbohydrates or i.v. glucose may be administered.

- In case of asymptomatic Level 1 hypoglycaemic events, the plasma glucose testing will be repeated at least every 15 min until plasma glucose is ≥ 70 mg/dL.

- In case of an elevated plasma glucose concentration (PG > 180 mg/dL) outside the meal test and basal insulin suspension procedure (see Section 8.8.1 for respective treatement), the subject may be treated to lower the plasma glucose level within the normal range if deemed necessary by the investigator.

- Treatment of hypoglycaemia during the meal test and pump suspension procedure will be as described in Sections 8.4 and 8.8.1.

8.9.2 Laboratory Assessments

The safety parameters that will be determined at the safety laboratory are listed in Table 5.

The safety laboratory will perform a first check on their values for safety parameters and flag any values outside the reference range. The Investigator must evaluate all results outside the reference range (clinically significant or not clinically significant). Before the Investigator starts the trial (i.e. obtains informed consent from the first subject), the laboratory reference ranges must be available in the Investigator's Trial File. The results provided by the safety laboratory will be part of the trial database.

Table 5 Routine laboratory safety tests

Haematology	
Haematocrit	Leucocytes
Haemoglobin	Neutrophile granulocytes (total count and relative)
Erythrocytes	Lymphocytes (total count and relative)
Mean corpuscular volume (MCV)	Monocytes (total count and relative)
Mean corpuscular haemoglobin (MCH)	Eosinophile granulocytes (total count and relative)
Mean corpuscular haemoglobin concentration (MCHC)	Basophile granulocytes (total count and relative)
Thrombocytes (platelets)	
Biochemistry	
Sodium	Uric acid
Potassium	Total protein
Calcium	Albumin
Chloride	Total bilirubin
Phosphate	Creatine kinase
Creatinine	Alkaline phosphatase
Urea	Gamma-glutamyltransferase (γ-GT)
AST (aspartate aminotransferase, GOT)	Lactic dehydrogenase (LDH)
ALT (alanine aminotransferase, GPT)	
Total cholesterol	High-density lipoprotein (HDL) cholesterol
Low-density lipoprotein (LDL) cholesterol	Triglycerides
Coagulation (screening only)	
International normalized ratio (INR)	Activated partial thromboplastin time (APTT)
Urinalysis	
Protein	Leucocytes
Glucose	pH
Erythrocytes	Ketones
Infectious serology (screening only)	
Hepatitis B surface antigen	HIV-1/2 combi
Hepatitis C antibodies	
Other	
HbA1c (screening only)	serum β-HCG (females only; screening only)
C-peptide (screening only)	

Pregnancy test

For all female participants, a pregnancy test will be performed at the safety laboratory on a blood (serum) sample obtained at the screening visit and at Visits 2-4 from a urine sample at the trial site. The pregnancy test will be performed according to local regulation.

8.10 Other Assessments and Dietary Requirements

Demography

- Age
- Sex
- Race

Concomitant medication

A **concomitant medication** is any medication, other than the IMPs and current diabetes treatment (including insulins for diabetes therapy wash-out), which is taken during the trial, including screening and follow-up periods.

Details of any concomitant medication must be recorded at trial entry (i.e. at screening). Any changes in concomitant medication must be recorded at each visit as they occur. The information collected for each concomitant medication includes (at a minimum) trade name or generic name, indication, start date and stop date or continuation. A change in medication due to an AE must be recorded and reported according to Section 9. If the change in medication influences the subject's eligibility to continue in the trial, the Sponsor and monitor must be informed.

Diagnosis of diabetes and current diabetes treatment

- Date of diagnosis of diabetes
- Current diabetes treatment [start date, product name(s), dose(s)]

Body measurements

- Height (cm), without shoes
- Body weight (kg), only wearing underwear
- Body mass index (kg/m^2) calculated by the Investigator based on height and body weight (body weight/height^2)

Alcohol breath test

An alcohol breath test will be performed using an alcohol meter (‰) by standard procedures at the trial site.

Screening for drugs of abuse

At the screening visit, a urine quick test for the presence of drugs of abuse (e.g. amphetamine, barbiturates, benzodiazepines, cannabis, cocaine, methadone, methamphetamine, opiates,

phencyclidine and tricyclic antidepressants) will be performed at the trial site from at least 5 mL fresh mid-stream urine using a stick.

Fasting

Fasting is defined as abstinence from food and beverage consumption (other than water) for at least 10 hours. Intake of rapidly absorbable carbohydrates (not more than 20 g carbohydrate) will be allowed if necessary to prevent hypoglycaemia.

Subjects should arrive fasting prior to screening and follow-up and should be fasting prior to dosing at the dosing visit.

Dietary Requirements

No specific nutritional regimen is required during the outpatient periods of the trial.

During the inpatient periods, specific dietary restrictions apply. During the inpatient periods, consumption of foods or drinks other than those served at the clinical unit is prohibited.

The dinner meals on Day -1 and Day 1 will be identical pre-defined meals.

The liquid meal for the meal test procedures will be identical on all meal test days and the relation of nutrients as described in Section 8.8.1.

All other meals during the in-house period are free-choice meals, i.e. meals (and snacks) can be chosen by the subject from a list of meals given in a menu.

Intake of the liquid meal on Day 1 will be supervised by the study staff and the consumption will be documented as described in Section 8.8.2.

8.11 Volume of Blood Sampled during Trial

A total amount of approximately 400 mL blood will be drawn from each subject during the trial.

Additional blood samples may be drawn at the discretion of the Investigator (e.g. glucose for safety).

Blood samples storage

All samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

The pharmacokinetic samples will be stored for up to maximum of 1 year following last subject last visit. All other samples will be destroyed at the latest after finalisation of the clinical trial report.

9 ADVERSE EVENTS

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for the appropriate medical care of subjects during the study.

Investigators must document their review of each laboratory safety report.

If a subject's IMP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF.

9.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a trial subject administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Note: This includes also events that occur after the subject has signed the informed consent.

AEs include:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory abnormality which is clinically significant, i.e. any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be recorded as AEs:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened after the subject has signed the informed consent.
- Pre-existing conditions which had started before the subject signed the informed consent. This also applies to previously unknown conditions which have been found as a result of assessments done as part of the study procedures (pre-existing conditions should be reported as medical history or concomitant illness).

Treatment Emergent Adverse Event (TEAE)

A TEAE is an AE that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.

In this trial, AEs occurring from first dosing until the follow-up visit will be considered as treatment emergent.

Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect, or
- events that may require intervention to prevent one of the above listed outcomes.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

An AE, fulfilling one of the criteria of seriousness and being assessed as related to IMP application, the nature or severity of which is not consistent with the applicable reference document (e.g. IB for an unapproved investigational product or package leaflet/SmPC for an approved product). Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

Other Significant Adverse Events

Other significant adverse events will be defined as marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events (4).

Intensity of an Adverse Event

The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A ‘severe’ reaction does not necessarily deem the AE as ‘serious’ and a SAE may not be ‘severe’ in nature.

Causality relationship to IMP

The causality of each AE should be assessed by the Investigator according to the following classification:

Probable: Good reason and sufficient documentation to assume a causal relationship.

Possible: A causal relationship is conceivable and cannot be dismissed.

Unlikely: The event is most likely related to aetiology other than the trial product.

Outcome of an Adverse Event

The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

Recovered/resolved: The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.

Recovering/resolving: The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial.

Recovered/resolved with sequelae: The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.

Not recovered/ not resolved: The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.

Fatal: This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/ resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.

Unknown: This term is only applicable if the subject is lost to follow-up.

9.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported from the time the subject signs the informed consent until the end of the post-treatment follow-up period. At each contact with the site (visit or telephone, excluding safety visits, where the subject is not seeing the Investigator or his staff (e.g. visits to the laboratory)) the subject must be asked about AEs.

All AEs, either observed by the Investigator or reported by the subject, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made the Investigator should record each sign and symptom as individual AEs.

All AEs must be recorded by the Investigator. One single Adverse Event Form must be used per AE from start to resolution. For SAEs, the Serious Adverse Event Form must also be completed.

AE information should include the following:

- AE term
- Date and time of onset and resolution
- Date of Investigator's first information on the (S)AE (will not be collected in the CRF)
- Seriousness
- Severity
- Causal relationship with IMP
- Interruption or withdrawal of treatment with IMP and other measures taken
- Outcome

The date and time of the last contact with a subject subject will be entered for any ongoing AE where outcome is "recovering/resolving" or "not recovered/not resolved".

The Investigator or his/her staff must alert the Sponsor, or its designee, of any SAE as soon as practically possible. The Investigator must report initial information in writing (email) on all SAEs to the responsible medical monitor of the Sponsor immediately (within 24 hours) and to the Sponsor's responsible pharmacovigilance unit after obtaining knowledge about the event.

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The Sponsor must inform the Competent Authorities and IRBs/IECs in accordance with the local requirements in force and ICH guideline for GCP. The trial monitor must be informed accordingly.

Although all AEs are recorded in the eCRF/designated data transmission methods after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received IMP. However, if an SAE occurs after signing informed consent, but prior to receiving IMP, AND when causality is considered at least possible in relation to a study procedure, then it MUST be reported.

9.3 Follow-up of Adverse Events

Follow-up procedures may be different based on the nature (diagnosis, severity, seriousness) of the AE and will follow Profil's SOP on (S)AE Handling and Reporting.

Non-serious AEs classified as severe or possibly/probably related to trial product will be followed until the subject has "recovered" or "recovered with sequelae" and all queries have been resolved.

Note: Cases of chronic conditions, cancer or AEs ongoing at time of death (i.e. a subject dies from another AE), can be closed with an outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering", when the subject has completed the post-trial follow-up period (1 week after last dosing) and is expected to recover by the Investigator .

All other non-serious AEs will be followed up until the outcome of the event is "recovering", "recovered", "recovered with sequelae" or until the end of the post-treatment follow-up period (1 week after last dosing), whichever comes first, and until all queries related to these AEs have been resolved.

The Investigator shall follow up on all SAEs until the outcome of the event is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved, even after trial completion (LSLV). Note: Cases can be closed with an outcome of "recovering" when the subject has completed the trial and is expected by the investigator to recover.

Follow-up actions for all SAEs will be determined after internal review and/or sponsor review.

The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up the AE Form and SAE Form have to be used and reporting timelines follow those of a SAE.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from or completed the study. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to IMP or study participation, then the Investigator must promptly notify Lilly.

The Investigator must forward follow-up information on SAEs and if previously non-serious AEs become SAEs to the Sponsor/both, the authorized Sponsor's delegate for pharmacovigilance (Institute of Clinical Pharmacology) and the Sponsor (contact details are given in Section 9.2).

9.4 Hypoglycaemia

Hypoglycaemia will be recorded and documented using the dedicated Hypoglycaemia Episode form.

The classification and recording of hypoglycaemia in the trial will conform to the current ADA guidance (5).

- Level 1 hypoglycaemic event (Glucose Alert Value): is defined as a symptomatic or asymptomatic event with a measured plasma glucose concentration <70 mg/dL (<3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L), [equivalent to a glucose concentration of <63 mg/dL and ≥49 mg/dL when using whole blood calibrated results]

- Level 2 hypoglycaemic event (Clinically significant hypoglycaemia): is defined as a symptomatic or asymptomatic event with a measured plasma glucose concentration <54 mg/dL (3.0 mmol/L), [equivalent to a glucose concentration of <49 mg/dL when using whole blood calibrated results]

  For Level 1 and Level 2 hypoglycaemic events , the Investigator should also assess whether or not the event was accompanied by symptoms of hypoglycaemia (symptomatic or asymptomatic hypoglycaemic event).

- Level 3 hypoglycaemic event (**Severe hypoglycaemia**): A severe event characterized by altered mental and/or physical status requiring assistance. Subjects had either altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These events may be associated with sufficient hypoglycaemia to induce seizure or coma. Plasma or blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Severe hypoglycaemia will be regarded as SAE and should be recorded on AE and SAE forms.

Any severe hypoglycaemic episode will be accompanied by a narrative giving qualitative descriptions of timing of the episodes in relation to drug exposure, time of onset, time after last drug administration, time after meal, severity, duration, outcome of hypoglycaemia, dose of treatment.

9.5 Pregnancy

Female subjects must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

Pregnancy (maternal or paternal exposure to IMP) does not meet the definition of an AE. However, to fulfil regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and foetus.

9.6 Precautions

Normal precautions taken for a human trial, including the provision of emergency equipment, will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the subjects. During a subject's participation in the trial, the Investigator should ensure that adequate medical care is provided to the subjects for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the subject when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for LY900014 and Humalog®, please refer to the current version of the IB and the SmPC for Humalog® respectively.

9.7 Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Subjects should be instructed to contact the Investigator as soon as possible if he or she has a complaint or problem with the IMP so that the situation can be assessed.

10 RISK-BENEFIT ASSESSMENT

Potential Risks

Potential Benefits

Risk-Benefit Assessment

This study will not offer any direct benefits to the subjects participating in the study. The data from previous studies in healthy subjects and subjects with T1DM and T2DM have shown that LY900014 was well tolerated and the adverse drug reactions are in keeping with those reported for Humalog.

Potential risks associated with LY900014, derived from the known risks of insulin lispro (Humalog), are hypoglycaemia, hypersensitivity reactions (localised allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral oedema (Humalog package insert, 2015).

Notably, across all doses in the studies that have evaluated treprostinil[redacted] as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those AEs associated with systemic absorption of treprostinil, as described in the Remodulin package insert [redacted] The exposures of treprostinil in LY900014 for participants in ongoing and future clinical studies are expected to be much lower than those observed in the dose ranges previously explored with SC bolus administration of treprostinil. Accordingly, treprostinil exposure in diabetic subjects is generally below the detection limit (0.010 ng/mL) and is substantially lower (at least ~200-fold lower) than those observed in adults for the treatment of PAH. No known potential risks are associated with the microdoses of treprostinil in the LY900014 formulation (LY900014 IB).

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. Additionally, local and systemic toxicity profiles of Humalog and Remodulin do not suggest the potential for additive or synergistic toxicity.

The study includes inpatient procedures during which participants will be continuously monitored. Induced hyperglycaemia as well as in the event subjects experience hypoglycaemia during the procedures, these will be treated as described in Section 8.8.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY900014 is to be found in the Investigator's Brochure (IB).

11 DATA MANAGEMENT

Data Management is the responsibility of Profil Institut für Stoffwechselforschung GmbH, Neuss Germany.

The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

Additional information to the Trial Design will be specified in the form SDTM - Trial Design Domain Specifications.

11.1 Case Report Forms (CRFs)

For this trial an electronic CRF (eCRF) will be used.

The Data Management Department of Profil Institut für Stoffwechselforschung GmbH will provide the eCRF. All further information regarding the CRF and the data flow will be described and agreed on in the Data Management Plan.

12 MONITORING PROCEDURES

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial subjects are respected, (ii) that accurate, valid and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The monitor must be given direct access to the TIF and source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include to verify the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of subject records, the adherence to the protocol and the progress in subject enrolment.

Because no information that could reveal the identity of subjects may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitor will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitor during all visits.

Site Initiation Visit

During the Site Initiation Visit (SIV) the Sponsor and/or monitor will review information on the IMP, the protocol, the CRFs and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Sponsor's documentation on the SIV (e.g. power point presentation) should be filed by the Investigator.

Source Data Verification

Details on source data verification are specified in the Monitoring Manual.

13 STATISTICAL CONSIDERATIONS

Eli Lilly will be responsible for the derivation of the PK and GD endpoints and will provide the derived PK and GD endpoints to Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany. Profil will be responsible for the statistical analysis of the endpoints. The statistical planning and conduct of the analyses of the data will follow the principles defined in relevant ICH guidelines and the Sponsor's and Profil's SOPs. A general description of the statistical methods to be used is given in this chapter, specific details will be provided in the SAP. All statistical analyses performed at Profil will use SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), Version 9.4 or later. PK parameters, analysed by Eli Lilly, will use standard noncompartmental methods of analysis (Phoenix® version 6.3 or above).

13.1 Sample Size Calculation

A sample size calculation was performed based on the primary endpoint and an assumption of an SD of the primary endpoint of 78 min (crossover mean square error of ~55). A sample size of 24 subjects who complete the trial is considered to be sufficient to evaluate a difference between the treatments of 32 minutes with a power of 80%. Discontinued subjects may be replaced to ensure that 24 subjects complete the trial. To take account of discontinued subjects, 28 subjects will be enrolled in the trial. A replacement subject will be assigned to the same treatment sequence as the patient being replaced.

13.2 Selection of Subjects for Analyses

The following analysis sets are defined in accordance with the ICH-E9 (6) guidance:

Full Analysis Set (FAS)

The full analysis set (FAS) is based on the intention-to-treat principle and includes all subjects who were treated with IMP. Subjects will contribute to the evaluation 'as randomized'.

Modified FAS (mFAS)

The modified FAS includes all subjects of the FAS who complete the study according to the sequence/treatment to which they are randomized. Subjects will contribute to the evaluation 'as randomized'. Primary and secondary statistical analyses of PK and GD parameters will be conducted on the set of subjects who complete all treatment periods with the same dose and meal intake CCI [redacted]

Safety Analysis Set

The safety analysis set includes all enrolled subjects, whether or not they fulfilled all protocol requirements. Subjects in the safety set will contribute to the evaluation 'as treated'. The safety analysis will be based on the safety analysis set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing which IMP the subjects are assigned to. The blinding of the IMPs will be maintained for everyone involved in allocating subjects to the analysis sets until data are released for statistical analysis. Obviously erroneous data points may be excluded from the analyses or re-analysed (in case of e.g. serum concentrations). The decision to re-analyse or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator and the Trial Statistician.

The subjects or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database lock. The documentation will be stored together with the remaining trial documentation. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical study report.

Subjects withdrawn from the trial will be listed including the primary reason for withdrawal.

If deemed necessary further endpoints and/or analyses may be added to the SAP. Only analyses not specified in the SAP will be considered as post-hoc analyses.

All analyses will be fully detailed in the SAP.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

13.3 Statistical Methods

13.3.1 Pharmacokinetic Parameter Estimation

Subjects have measurable insulin lispro concentrations will be included in the analysis dataset for the PK analyses. PK analyses will be conducted using standard noncompartmental methods of analysis (Phoenix® version 6.3 or above) on a computer that meets or exceeds the minimum system requirements for these programs. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

Free serum insulin lispro concentrations will be used to calculate several PK parameters including: time to early half-maximal drug concentration (early 50% t_{max}), maximum observed drug concentration (C_{max}), time to maximum observed drug concentration (t_{max}), AUC from time 0 to 15 minutes [AUC(0-15min)], AUC from time 0 to 30 minutes [AUC(0-30min)], and AUC from time zero to 5 hours [AUC(0-5h)], Other parameters may be calculated as deemed

appropriate, such as partial AUCs, time to late half-maximal drug concentration (late 50% t_{max}) and AUC from time zero to infinity [AUC(0-∞)], etc.

For Day 1 (Missed Bolus following Meal): The PK parameters will be calculated using a change from baseline (CFBL), as defined as the bolus dose administration (B). For each day and period, the average of the two samples collected immediately prior to the correction bolus will represent as the 0-hour time point for each subject, and will be used to subtracting the baseline value from all post-dose insulin lispro measurements. The CFBL PK parameters would include: CFBL AUCs, and C_{max}.

For Day 2 (Basal insulin suspension): As each subject will suspend their own individual basal rate, insulin lispro concentration at the time of administration of the correction bolus may vary from being detectable to undetectable (<LLOQ). Due to this, the PK parameters will be calucated using the CFBL insulin lispro concentrations following the correction bolus (as described in the Day 1 analysis). An analysis using the raw insulin lispro concentration may be explored, if differences in insulin lispro concentration between treatments (LY900014 and Humalog) prior to the correction bolus are observed.

Additionally, an exploratory analysis may be conducted to assess the insulin lispro PK during the basal insulin suspension to hyperglycemia on Day 2. PK parameters that may be explored include the half-life ($t_{1/2}$) and apparent clearance (CL/F). The insulin lispro concentration time profile may be compared between LY900014 and Humalog during this time.

Although attempts will be made to adhere to the scheduled collection times, it is recognized that situations arise that may compromise sample collection at the scheduled times. Parameters will be individually calculated for each subject based on actual collection times and presented by summary statistics.

Individual and mean curves for the PK profiles will be plotted by treatment over the sampling period. Both the linear and the log-linear concentration scale will be used.

13.3.2 Glucodynamic Parameter Estimation

For each study day (Day 1: meal test procedure with missed meal bolus and Day 2: basal insulin suspension), the primary endpoint time to recovery from hyperglyemia after administration of a correction bolus will be determined per subject and period. The determination of the time to recovery after administration of a correction bolus will be calculated from the time of correction bolus administration until the time of the exact point of time when PG is 140 mg/dL, which will be determined using linear interpolation.

Similarly, for each study day, the key secondary glucodynamic endpoints include: glucose AUCs, PG_{max} and rate of change in PG will be determined.

The secondary endpoint rate of change in PG will be defined as the change in PG at the time of bolus IMP administration (B) to PG at 140mg/dl divided by the duration of time for this interval. based on individual measurements per subject, period and day.

The following secondary GD AUCs will be calculated per patient, period and day:

- the area under the PG curve, but above 140mg/dL from time of correction bolus to the time that the PG is 140mg/dl ($AUC_{B\text{-}tPG140}$) and
- the area under the PG curve but above 180mg/dL from time of the correction bolus to the time that the PG is 180mg/dl ($AUC_{B\text{-}tPG180}$).

The AUCs will be calculated using the linear trapezoidal rule and using the actual times along with the time when PG is 140 mg/dL or 180mg/dL, which will be determined using linear interpolation. Additionally, calculation of baseline corrected AUC (iAUCs) using the PG at the administration time of the correction bolus may be explored to address possible inter-occasion variability.

The secondary GD endpoint PG_{max} will be determined individually per subject, period and day based on measured PG values.

Evaluation of the exploratory endpoint time to hyperglycemia after basal insulin suspension will be performed on day 2. The time will be calculated using the time of the basal insulin suspension until the time of the exact point of intersection with the target margin of 240 mg/dL.

Individual and mean curves for the PD profiles will be plotted by treatment over the sampling period.

13.4 Statistical Analysis

13.4.1 Analysis of the Primary Endpoints time to recovery from hyperglycaemia

Subjects who did not keep identical insulin lispro doses for LY900014 and Humalog for each day and period or had differences in the test meal will be excluded from the statistical analysis of the GD parameters.

For the primary endpoint, comparison between the treatments will be peformed per day (Day 1: meal test procedure with missed meal bolus, Day 2: basal insulin suspension) using a linear mixed model analysis of variance (ANOVA) with raw endpoint as response, treatment, period and sequence as fixed effects and patient within sequence as a random factor. Within the model, least squares means of LY900014 and Humalog®, differences in LSmeans and the corresponding 95% CI for the treatment difference will be estimated. The p-value on the difference between least squares (LS) means will be used to determine statistical significance. The treatment ratio and 95% CI for the ratio will be calculated using Fieller's theorem (Chow SC, Liu JP. 2009).

13.4.2 Analysis of the Secondary GD Endpoints

Subjects who did not keep identical insulin lispro doses for LY90014 and Humalog® for each day and period or had differences in the test meal will be excluded from the statistical analysis of the PK parameters.

Log-transformed PG AUCs and PG_{max} will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog, and their corresponding 95% CIs of the ratios using the mixed-effects model that includes treatment (LY900014, Humalog), period and sequence as fixed effects and subject as a random effect. The analysis will be performed separated by day (Day 1: meal test procedure with missed meal bolus , Day 2: pump suspension). In case of determination of baseline corrected AUCs to address possible inter-occasion variability, iAUCs will be analysed using the same model. Analysis of iAUCs will be based on untransformed endpoints, if negative values occurred. In this case, LSmeans, treatment differences in LSmeans, and corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The same model without log transformation will be used for the analysis of the rate of change in PG and exploratory GD time parameters. Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between least squares (LS) means will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow SC, Liu JP. 2009).

13.4.3 Analysis of the Secondary PK Endpoints

Subjects who did not keep identical insulin lispro doses for LY90014 and Humalog for each day and period will be excluded from the statistical analysis of the PK parameters.

Log-transformed AUCs, and C_{max}, for insulin lispro will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog, and their corresponding 95% CIs of the ratios using the mixed-effects model that includes treatment (LY900014, Humalog), period and sequence as fixed effects and subject as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters (time to early half-maximal drug concentration [early 50% tmax], and time of C_{max} [t_{max}], [late 50% tmax if calculated]). Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between least squares (LS) means will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow SC, Liu JP. 2009).

13.4.4 Analysis of Safety Endpoints

Safety endpoints will be based on all reported adverse events. Allocation of adverse events to IMP will be conducted from start of study insulin pump with IMP on Day 1 until study pump disconnection on day 2.

All adverse events will be listed and summarised by descriptive statistics. All serious adverse events will be reported.

13.4.5 Subject Disposition

Subject disposition will be tabulated including the numbers of screened subjects, screening failures, subjects exposed to trial product, withdrawals including reason, subjects completing the trial and subjects in the FAS.

13.4.6 Other Measurements and Criteria

The analysis of all other measurements and criteria will be described in the SAP.

13.5 Interim Analysis

No interim analysis is planned. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

The Lilly study team is unblinded; the investigator shall remain blinded until database lock is achieved. Data may be analyzed by the Lilly study team while the trial is ongoing but no changes to the study design are planned. No assessment committee will be formed.

14 INDEPENDENT ETHICS COMMITTEE AND COMPETENT AUTHORITY

The trial will be conducted according to Profil's and /or the Sponsor's written instructions (SOPs, working instructions or process descriptions). Content and definitions of Profil's written instructions are based on the following relevant binding documents and standards

- the German Medicinal Products Act (AMG)
- the German GCP ordinance (GCP-Verordnung)
- the Declaration of Helsinki (7)
- the International Conference on Harmonisation Good Clinical Practice (ICH GCP) (8)

The trial will be conducted in accordance with the above mentioned standards.

14.1 Independent Ethics Committee

Written favourable opinion must be obtained from the responsible independent ethics committee (IEC) prior to commencement of the trial. Clinical trial submission and reporting requirements before, during and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect subject safety or the trial integrity (substantial amendments) must not be implemented before favourable opinion has been obtained, unless necessary to eliminate hazards to the subjects. Non-substantial amendments do not require favourable opinion by the IEC but the respective IEC will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the IEC. The records should be filed in the Sponsor's Trial Master File.

14.2 Informed Consent Process for Subjects

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline (8) and the requirements in the Declaration of Helsinki (7).

Prior to any trial-related activity, the Investigator must give the subject oral and written information in a form that the subject can read and understand about all aspects of the trial that are relevant to the subject's decision to participate. The subject will be given ample time to decide whether or not to participate in the trial.

The subject must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated Informed Consent Form must be obtained from the subject prior to any trial-related activity. The Informed Consent Form must also be signed and dated by the physician who conducted the informed consent procedure. All subjects will be provided with a copy of their own signed and dated informed consent form and with any additional subject information.

The responsibility for taking informed consent must remain with that of a research physician.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the Investigator must inform the subject in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the Informed Consent Form may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favourable opinion from IEC, and the Investigator has to ensure that the amended consent form is signed by all subjects subsequently entered in the trial and those currently in the trial, if affected by the amendment.

14.3 Competent Authority

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's Trial Master File.

14.4 Premature Termination of the Trial

The Sponsor, Investigator or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons.
- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical trial.
- A decision of the Sponsor to suspend or discontinue investigation of the IMP.

If a trial is prematurely terminated or suspended, the Investigator should promptly inform the subjects and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IEC and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IEC in case it will have an impact on the planned follow-up of the subjects who have participated in the trial. Necessary actions needed to protect the subjects should be described.

15 ADMINISTRATIVE MATTERS

15.1 Deviations from the Protocol

A deviation from the protocol is in general an unplanned non-compliance with the protocol that is not implemented or intended as a systematic change. The Investigator, or person designated by the Investigator, should document and explain any deviation from the protocol and inform the Sponsor and/or monitor. The deviation must be evaluated for its root cause and classification (important/non-important). Corrections (if possible) and/or corrective/preventive actions are to be documented and implemented. The documentation must be kept in the TIF and the Sponsor's Trial Master File. Each deviation is listed in a deviation log.

15.2 Essential Documents

Essential Documents, as outlined in ICH GCP Chapter 8, are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the Investigator/institution and Sponsor sites in a timely manner can greatly assist in the successful management of a trial by the Investigator, Sponsor, and monitor. These documents are also the ones that are usually audited by the Sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

Trial files should be established at the beginning of the trial, both at the Investigator's site (Investigator Site File) and at the Sponsor's office (Trial Master File). A final close-out of a trial can only be done when the monitor has reviewed both Investigator/institution and Sponsor files and confirmed that all necessary documents are in the appropriate files.

15.3 Responsibilities

The trial related responsibilities are defined in the trial specific Responsibility Split List, which is an essential part of the trial contract. In this document the distribution of responsibilities between Sponsor, Profil and third parties (e.g. contract laboratories) is specified.

The Investigator is accountable for the conduct of the trial according to the approved protocol, ICH-GCP (8) and Declaration of Helsinki (7). For responsibilities delegated, the Investigator should maintain a list of appropriately qualified persons to whom he has delegated specified significant trial-related duties. The Principal Investigator will acknowledge receipt of the IB, discuss and approve the protocol and review and sign the Integrated Clinical Trial Report.

The Investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Investigator will prevent any unauthorized access to data or any other processing of data against applicable law.

Pharmacovigilance tasks are the responsibility of *Eli Lilly* and are outlined in detail in the Safety Management Plan for this trial.

15.4 Reports and Publications

The Principal Investigator of the trial will review and sign the clinical trial report on behalf of Profil Institut für Stoffwechselforschung GmbH. A summary of the final clinical trial report will be submitted to the IEC and Competent Authority.

According to the Declaration of Helsinki (7) Investigators and Sponsors 'have ethical obligations with regard to the publication and dissemination of the results of research'.

The trial design and results may be published as one or more original research manuscripts / abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors (ICMJE) (9).

Participating subjects will not be identified by name in any published reports about the clinical trial.

15.5 Audits and Inspections

In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the informed consent form signed by the subject.

15.6 Retention of Clinical Trial Documentation

Profil will maintain the subject's medical file according to local regulations.

Profil will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. Profil should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the TIF and a copy of the clinical report. The documents will be retained for a period of at least 15 years at archives by Profil, or its sub-contractor. After this period, the Sponsor will be contacted and their advice sought on the return or further retention of the trial records.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

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APPENDIX I - AMENDMENTS

Amendment a

Overall Rationale for the Amendment:

This protocol was amended to comply with BfArM recommendations.

Section # and Name	Description of Change
6.3. Exclusion Criteria	Updated hypersensitivity criterion to include active substance or to any of the excipients to exclusion criterion 1
	Added 5 half-lives to exclusion criterion 3
	Updated blood pressure range to acceptable values of exclusion criterion 12
6.5.1. Discontinuation of Inadvertently Enrolled Subjects	Deleted section
9.4. Hypoglyceamia	Removed reference to adverse event

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