Statistical Analysis Plan I8B-MC-ITST (V1)

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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STATISTICAL ANALYSIS PLAN

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

Trial Phase: 1

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SIGNATURES

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TABLE OF CONTENTS

Page

List of Tables

List of Figures

List of Appendices

LIST OF ABBREVIATIONS

Please note that definitions and abbreviations of pharmacokinetic and efficacy parameters are not contained in this list. They can be found in Section 4.2 and 4.3 of this SAP. Abbreviations for laboratory safety parameters, which are only used once in Section 4.6.2, are also not listed here.

ADA	American diabetes association
AE	adverse events
AESI	Adverse Event of Special Interest
ANOVA	analysis of variance
B	Bolus administration
BP	blood pressure
BMI	body mass index
CFBL	Change from baseline
CI	confidence interval
CSII	Continuous Subcutaneous Insulin Infusion
CSR	Clinical study report
CV	coefficient of variation
DBR	database release
ECG	electrocardiogram
eCRF	electronic case report form
eVAS	electronic visual analogue scale
FAS	full analysis set
FDA	Food and Drug Administration
FSFV	First subject first visit
FUP	follow-up
GCP	Good clinical practice
GD	Glucodynamics
GIR	glucose infusion rate
HbA1c	glycated haemoglobin
HR	heart rate
iAUC	baseline corrected AUC
IC	informed consent

ICH	International council for harmonisation
IMP	Investigational medicinal product
INR	International normalised ratio
i.v.	Intravenous(ly)
LLOQ	lower limit of quantification
LS	Least squares
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full analysis set
NIMP	Non-investigational medicinal product
PAH	Pulmonary arterial hypertension
PD	pharmacodynamic
PG	plasma glucose
PK	pharmacokinetics
QTc	corrected QT interval
QTcB	Qtc corrected by Bazett
SAE	serious adverse event
SAP	statistical analysis plan
SFAS	safety analysis set
s.c.	subcutaneous(ly)
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse events
T1DM	type 1 diabetes mellitus
U	Units

1 INTRODUCTION

1.1 Objectives of Statistical Analysis Plan

The statistical analysis plan (SAP) describes in detail the statistical analyses to be conducted on the data from the Phase 1 trial I8B-MC-ITST.

The SAP elaborates on the statistical analyses outlined in the protocol, and any deviations are clearly stated in the present SAP including the reason for the deviation. The trial will be evaluated according to the specifications given in this analysis plan. However, deviations from the SAP may be necessary in which case the nature of and the reason for the deviations will be documented and explained in the clinical study report (CSR).

1.2 Scope

This SAP is based on the finalized protocol Version 2.0, dated 17-Jan-2020.

2 STUDY OBJECTIVES AND ENDPOINTS

The purpose of this 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 when consuming a meal or when there is suspension of insulin delivery e.g. due to a malfunction of the insulin pump in subjects with Type 1 Diabetes Mellitus (T1DM).

Table 1 shows the objective and endpoints of the study.

Table 1 Objectives and endpoints

Objectives	Endpoints
Primary	**PD endpoints:**
• 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	• Time to recovery from hyperglycemia (time of correction bolus to time when plasma glucose [PG]) = 140 mg/dL)
Secondary	**PK endpoints:**
• To compare the pharmacodynamics and insulin lispro pharmacokinetics following a correction bolus of LY900014 vs. Humalog® during recovery from hyperglycaemia following a missed meal bolus. • To compare the pharmacodynamics and insulin lispro pharmacokinetics following a correction bolus of LY900014 vs. Humalog® during recovery from hyperglycaemia after basal insulin suspension.	• 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. **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)

Objectives	Endpoints
	• 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
Exploratory • To assess the blood glucose response after basal insulin suspension for LY900014 vs. Humalog®.	• Time to hyperglycaemia (PG > 240 mg/dL) after basal insulin suspension • Peak ketone concentration after basal insulin suspension
Safety • To assess the safety and tolerability of LY900014 and Humalog®.	**Safety endpoints:** • AEs **Safety assessments:** • Hypoglycaemic episodes • Laboratory safety parameters • Physical examination • Vital signs • ECG

3 STUDY DESIGN AND DESCRIPTION

3.1 Study Design

The study is a phase 1, single-centre, randomised, 2-treatment, subject- and investigator-blind, 2-way cross-over trial in subjects with T1DM. The trial will be carried out in one center in Germany.

The study consists of a:

- informed consent (Visit 0)
- a screening visit (Visit 1)
- two in-house study visits with IMP administration (Visits 2 and 3)
- a follow–up (FUP) visit (Visit 4)

Figure 1 shows the study design of the study.

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. Randomisation 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. 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 randomisation 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 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 of IMP. 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 [redacted] 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 [redacted] 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 [redacted] 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.

Up to 28 subjects will be randomised in this trial to ensure that at least approximately 24 subjects complete both the periods to enable evaluation of the primary objective. The subjects will be

randomly allocated to one of two treatment sequences (LY900014 followed by Humalog® or Humalog® followed by LY900014).

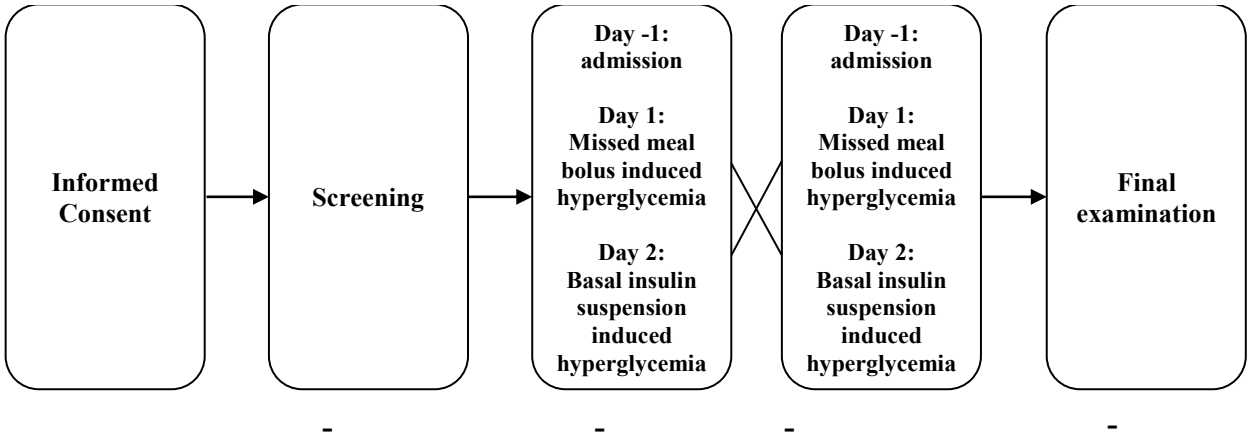

Figure 1 Study Design

The schedule of assessments performed at each visit is given in Appendix 1.

A description of inclusion and exclusion criteria is given in the protocol Sections 6.2-6.3.

3.2 Investigational Medicinal Products

Subjects will receive LY900014 followed by Humalog® or Humalog® followed by LY900014 as described in Table 2.

Table 2 Treatments administered

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

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

3.3 Planned Number of Participants

Up to 28 subjects will be randomised in this trial to ensure that at least approximately 24 subjects complete both the periods to enable evaluation of the primary objective.

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 randomised in the trial. A replacement subject will be assigned to the same treatment sequence as the subject being replaced.

Subject Replacement:

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.

Screening Failures:

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. Re-screening of screening failures is generally not allowed.

Planned number of sites:

One site in Germany:

- Profil Institut für Stoffwechselforschung GmbH in Neuss

3.4 Randomisation Code Creation

The Profil Institut für Stoffwechselforschung GmbH, 41460 Neuss, will generate the randomisation codes using the computer program CCI [redacted]

When a subject is randomised in the study, he/she must always be assigned to the lowest available randomisation number available from the randomisation list. Up to 28 subjects will be randomised to ensure that at least 24 can be evaluated.

Randomisation numbers will be as follows:

- Randomisation numbers starting with 101, 102, 103…

A replacement subject will be assigned to the same treatment as the subject being replaced. For randomisation numbers for replacements 100 will be added to the randomisation number of the subject being replaced.

- Corresponding randomisation numbers for replacements: 201, 202, 203…

4 ANALYSIS VARIABLES

4.1 Demographic and Baseline Characteristics

The following demographic variables and baseline characteristics will be collected at screening:

- Age
- Sex
- Race
- Body Weight, Height, Body mass index (BMI)
- Diabetes duration, diagnosis of diabetes and current diabetes treatment
- Concomitant illness and medical history
- Serology (hepatitis B surface antigen, hepatitis C antibodies and human immunodeficiency virus -1/2 combi)
- Coagulation (International normalized ratio and activated partial thromboplastin time)
- N-(1-deoxy)-fructosyl-haemoglobin (HbA1c)
- Fasting C-Peptide
- Smoking & alcohol habits
- Serum β-HCG (females only)
- Drugs of abuse

The BMI will be calculated based on the height and weight measured at screening according to the following formula:

BMI [kg/m^2] = weight [kg] / (height [m] x height [m]).

HbA1c will be presented in % as well as in mmol/mol using the following conversion:

HbA1c (mmol/mol) = [HbA1c (%) – 2.15]*10.929.

Diabetes duration in years will be calculated as difference between year of informed consent was signed and year of diabetes diagnosis.

A medical history is a condition that started and ended prior to when the informed consent form (ICF) is signed. Concomitant illnesses present at the start of the trial and relevant medical conditions, which deemed to be relevant by the Investigator, will be recorded in the electronic case report form (eCRF) 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 as AE.

For all female participants, a pregnancy test will be performed at the safety laboratory in a blood (serum) sample obtained 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.

4.2 Assessments for Pharmacokinetics

Eli Lilly will be responsible for the derivation of the PK endpoints and will provide the derived PK endpoints to Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany.

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 ($AUC_{(0\text{-}15min)}$), AUC from time 0 to 30 minutes ($AUC_{(0\text{-}30min)}$), and AUC from time zero to 5 hours ($AUC_{(0\text{-}300min)}$). 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 ($AUC_{(0\text{-}\infty)}$), etc.

For Day 1 (Missed Bolus following Meal): The PK parameters will be calculated using change from baseline (CFBL), which is 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 the 0-min time point for each subject and will be used to subtract 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

calculated 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.

4.3 Assessments for Pharmacodynamics

Eli Lilly will be responsible for the derivation of the PD endpoints and will provide the derived PD endpoints to Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany.

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 hyperglycemia 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 PD 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 140 mg/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 140 mg/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.

4.4 Exploratory Endpoints

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.

The ketone concentration will be measured on Day 2. The peak of ketone concentration will be defined as the maximum of the measured ketone concentrations.

4.5 Safety Endpoint

4.5.1 Adverse Events

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 IMP, whether or not considered related to the IMP.

Note: This includes 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.

A Treatment Emergent Adverse Event (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 (basal rate) until the follow-up visit will be considered as treatment emergent.

A serious adverse event (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.

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

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).

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 (2).

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

- Mild
- Moderate
- Severe

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

The causality relationship to study treatment and study procedure of each AE will be assessed by the Investigator according to the following classification:

- Probable
- Possible
- Unlikely

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

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

AE information will include the following:

- AE term
- Date and time of onset and resolution
- Seriousness
- Severity
- Causal relationship to IMP
- Interruption or withdrawal of treatment with IMP and other measures taken
- Outcome

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); details are described in the trial specific Data Management Plan.

Missing date and time data will only be replaced if at least the year exists and will be replaced as follows:

- AE start date and time:
    - Month: 1 (January)
    - Day: 1
    - Hour: 0
    - Minute: 0
    - Second: 0
- AE stop date and time:
    - Month: 12 (December)
    - Day: 28, 29, 30 or 31 (last day of the month in the given year)

- Hour: 23
- Minute: 59
- Second: 59

Imputed dates and times will be within the time window from earliest possible start date/time to last possible end date/time. Imputed dates/times outside this time window must be adapted by earliest possible start date/time and last possible end date/time.

If the year is missing, then the date will not be imputed.

4.6 Assessments for Safety

4.6.1 Hypoglycaemic Events

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 (3):

- 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. The number of episodes and the percentage of exposed subjects having at least one episode will be provided.

4.6.2 Laboratory Safety Parameters

If not otherwise stated the following assessments will be performed at screening as well as during FUP:

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
Urinalysis	
Protein	Leucocytes
Glucose	pH
Erythrocytes	Ketones

4.6.3 Electrocardiograms

A standard 12-lead ECG will be performed. An ECG will be performed at screening and FUP.

ECG parameters (Heart rate, PR, 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 the screening visit will 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.

4.6.4 Vital Signs

An examination of the following vital signs will be performed at screening, dosing visits (Day -1 and 2) and FUP.

- Diastolic and systolic blood pressure (BP) is measured after at least 5 min rest in a supine position.
- Pulse (beats per min) measured after at least 5 min rest in a supine position
- Body temperature, tympanic (°C).
- Respiratory frequency

In addition to the pre-specified assessments in protocol Section 2, BP and pulse may be assessed at any time during the trial at the discretion of the Investigator.

4.6.5 Physical Examination

An examination of the following body systems will be performed at screening, dosing visits (Day -1 and 2) and FUP:

- 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.

4.6.6 Plasma Glucose for Safety

During the trial, plasma glucose levels will be monitored at the trial site by CCI Glucose Analyzer for safety. At the discretion of the investigator, additional blood glucose measurements for safety may be made when there is a suspicion of a hypoglycemic or hyperglycemic episode.

4.7 Other Assessments

The following variables will be evaluated:

- Concomitant medication
- Body Weight
- Pregnancy test (dipstick)
- Alcohol breath test
- Amount of carbohydrates at standard liquid meal

A concomitant medication is any medication, other than the IMPs, 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.

For all female participants, a pregnancy test will be performed at the safety laboratory in a urine sample at the screening visit and from a urine sample at the trial site at Day -1 of Visits 2 and 3 and at follow-up.

An alcohol breath test will be performed at screening and Day -1 using an alcohol meter (‰) by standard procedures at the trial site.

The amount of carbohydrates at standard liquid meal will be measured at both dosing visits at Day 1.

5 STATISTICAL METHODOLOGY

5.1 Analysis Sets

The following analysis sets are defined in accordance with the International Council for Harmonisation (ICH)-E9 guidance (1):

Full Analysis Set (FAS)

The full analysis set (FAS) is based on the intention-to-treat principle and includes all subjects who were randomised. Subjects will contribute to the evaluation 'as randomised'. PK and PD listings (subjects, who are in the FAS, but not in the mFAS will be identified) and the subject disposition and demographic and baseline characteristics will be based on the FAS.

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 randomised. Subjects will contribute to the evaluation 'as randomised'. 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 as the PK parameters and GD response are dependent on the insulin dose which is individualized by subject.

Safety Analysis Set (SFAS)

The safety analysis set includes all enrolled subjects that have received IMP at least once (basal rate) - 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.

5.2 Protocol Deviations

During database cleaning, the unblinded SDTM data will be provided to Sponsor and to two Profil statisticians. This will still maintain the blinding as those individuals with access to the dataset will not be involved in the data base release (DBR) meeting. The statistical analysis will be provided on unblinded data before DBR.

Deviations from the protocol will be assessed as "important" or "non-important" in agreement with the sponsor. Protocol or procedure deviations are defined as "important" if they are likely to affect the outcome of the trial (e.g. effect on target variables). All other protocol and procedure

deviations are regarded as non-important. For important protocol and procedure deviations a description will be given in the CSR.

The subjects or observations to be excluded and the reason for their exclusion will be documented. Lilly's SOP for data exclusion will be followed. A sensitivity analysis may be conducted to assess the impact of data exclusion on the analysis. The reason for exclusion of subjects and details of the sensitivity analysis will be described in the CSR.

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

In any case all decisions to correct or exclude values must have a reasonable foundation and must be documented in the meeting minutes.

New NTFs, protocol and procedure deviations may be written after the meeting as a result of findings and decisions during the DBR meeting.

The blinded review is completed after signing the DBR meeting minutes prior to database lock.

5.3 Coding

AEs, medical history, and concurrent conditions will be coded using MedDRA as described in the Data Management Plan.

Concomitant medication will be coded using the drug record number from the World Health Organization (WHO) dictionary.

The used version numbers will be documented in the database.

5.4 Missing, Unused and Spurious Data

All available data will be included in data listings and tabulations. Unless otherwise specified in Section 4, no imputation of values for missing data will be performed. Imputed values will be presented in data listings and will be flagged.

Missing statistics will be presented as "NC" (not calculable). For example, if individual values are 0, the geometric mean cannot be calculated and will be presented as "NC".

Variable specific information for imputing missing data is given in Section 4.

5.5 Presentation of Results

5.5.1 Presentation of Summary Statistics and Individual Data

In general, continuous endpoints are summarized by the arithmetic mean, geometric mean, median, standard deviation, coefficient of variation (CV), geometric coefficient of variation, and minimum and maximum. Categorical variables will be presented using descriptive summary statistics including number of subjects and percentages. Percentages of subjects will be based on non-missing values.

All PK and PD endpoints will be summarised by treatment (LY900014 and Humalog) and dosing day (Day 1 and 2) using descriptive statistics and will be provided by Lilly using their SOP. All summary PD and PK parameters and mean plots will be presented for all subjects in the mFAS, which is reflective of the subjects used in the statistical analysis.

Individual PK and PD profiles will be plotted by treatment and dosing day. Individual profiles will be presented for all available data (FAS). Similarly, individual listing of PK and GD parameters will be presented for all subjects. The presentation of individual profiles and listings will be provided in the appendix of the CSR.

The safety endpoint and all tolerability assessments will be summarised using frequency tables or descriptive statistics and will be provided by Profil. For numeric data, individual as well as minimum and maximum values will be presented with the same number of decimal places as the raw data. Descriptive statistics, such as arithmetic mean and median values will be presented with an additional decimal place and standard deviation data with two additional decimal places as the raw data.

5.5.2 Presentation of Hypothesis Tests

Mixed effect models will be performed between LY900014 and Humalog® using SAS procedure PROC MIXED. Least square means (LS-means), LS-mean differences or ratios, corresponding confidence intervals (CIs) and p-values will be presented.

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.

5.5.3 Baseline Definition

If not stated otherwise baseline is defined as the last assessment prior to first drug intake unless otherwise stated.

PK parameters for Day 1 (Missed Bolus following Meal): For each day and period, the average of the two samples (pre-bolus) collected immediately prior to the correction bolus will represent as the 0-min time point for each subject, and will be used to subtracting the baseline value for all post-dose insulin lispro measurements.

PK parameters 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 calculated using the CFBL insulin lispro concentrations following the correction bolus (as described in the Day 1 analysis above).

The calculation of baseline corrected AUC (iAUCs) may be explored to address possible inter-occasion variability. If conducted, the average of the two samples (pre-bolus) used to confirm the high glucose threshold (<240mg/dl) which was collected immediately prior to the correction bolus will represent as the 0-min time point for each subject, and will be used to subtracting the baseline value for all post-dose glucose measurements.

5.6 Analysis and Presentation of Demographic and Baseline Characteristics

Demographic and baseline characteristics will be presented for all subjects in the FAS.

Individual demographic and background characteristics will be presented together with standard descriptive statistics as described above and will be presented in subject data listings.

The pre-existing conditions and medical history will be summarized using frequency tables. The presentation will be done by system organ class (SOC) and preferred term, ordered in alphabetic order.

5.7 Analysis of Primary Endpoints Time to Recovery from Hyperglycaemia

The PD parameters will be determined and analyzed using software SAS Version 9.4.

Subjects who did not keep identical insulin lispro doses for LY900014 and Humalog® for each day and period or had differences in the consumption of the test meal will be excluded from the statistical analysis of the PD parameters. Additionally, subjects which required a rescue insulin dose during the treatment assessment period would be excluded in the analysis for both treatments (LY900014 and Humalog) periods for that day (missed bolus following meal or basal insulin suspension) since an accurate comparison of the treatment difference would not be possible. Subjects excluded from the analysis will be identified by Lilly.

For the primary endpoint, comparison between the treatments will be performed 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 subject within sequence as a random factor.

Within the model, least squares means of LY900014 and Humalog®, differences in LS-means and the corresponding 95% CI for the treatment difference will be estimated. The p-value on the difference between 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 [4].

5.8 Analysis of Secondary PD Endpoints

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 PD parameters.

Log-transformed PG AUCs and PG_{max} will be evaluated to estimate geometric LSmeans, 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 within sequence as a random effect.

Within the model the LS mean for each treatment as well as the difference of the LSmeans between the treatment groups and corresponding 95% CI will be calculated and exponentially back-transformed in order to find the estimated ratio between the insulin formulations and corresponding 95% CI.

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 (iAUC) 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, LS-means, treatment differences in LS-means, and corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between 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.

The same model without log transformation will be used for the analysis of the rate of change in PG and exploratory PD time parameters. LS-means, treatment differences in LS-means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-

value on the difference between 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 [4].

5.9 Analyses of PK Parameters

Analysis of the PK parameters will be done using software SAS Version 9.4.

Subjects who did not keep identical insulin lispro doses for LY900014 and Humalog® for each day and period will be excluded from the statistical analysis of the PK parameters. Additionally, subjects which required a rescue insulin dose during the treatment assessment period would be excluded in the analysis for both treatments (LY900014 and Humalog) periods for that day (missed bolus following meal or basal insulin suspension) since an accurate comparison of the treatment difference would not be possible.

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 within sequence 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% t_{max}], and time of C_{max} [t_{max}], [late 50% t_{max} if calculated]). LS-means, treatment differences in LS-means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between 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 [4].

5.10 Analyses of Safety Parameters

Safety endpoints will be presented for all subjects in the safety analysis set (SFAS).

Safety of the treatment will be evaluated by AEs, hypoglycaemic events, laboratory tests, vital signs, ECG and physical examination.

Safety results will be presented using descriptive statistics by visit/treatment and in subject data listings. In addition, listings of abnormal data will be presented.

5.10.1 Analysis of Adverse Events

All AEs will be presented by individual listings and non-hypoglycaemic TEAEs (TEAEs in this section are non-hypoglycaemic; severe hypoglycaemia will be taken in account) will be presented using summary tables by treatment. The following summary tables will be presented:

(1) Overview of Incidence of TEAEs including:

- Number of subjects at risk
- Incidence and number of TEAEs
- Incidence of deaths
- Incidence and number of serious TEAEs
- Incidence and number of other significant TEAEs
- Incidence and number of severe TEAEs
- Incidence and number of drug related TEAEs (possibly or probably related to IMP as judged by the investigator)

The presentation will be done by treatment.

(2) TEAEs by MedDRA system organ class (SOC) and preferred term within each SOC and preferred term as well as in total including incidence and number of TEAEs. The presentation will be done by treatment. SOCs and preferred terms will be presented in alphabetic order.

(3) TEAEs by SOC and preferred term and by severity, relationship, seriousness, outcome, action taken with study drug due to this TEAE and other action due to this TEAE. The presentation will be done by treatment. SOCs and preferred terms will be presented in alphabetic order. Within each category the presentation will be done from the lowest to the highest subcategory.

(4) Separate tables for SAEs (in case of more than 2 SAEs).

The incidence of TEAEs will be presented with the number and percentage of participants affected. Percentages will be derived as ratio of number of participants affected and number of participants at risk multiplied by 100.

The following will be included in the listing of AEs:

- Screening and randomisation number
- Gender, age, race and weight

- Event number
- Treatment
- SOC and PT term
- Event term
- Start date and time
- End date and time
- Last dose date and time
- Seriousness
- Severity
- Outcome
- Relationship to IMP
- Relationship to study device
- Action taken with study drug due to this AE
- Action taken with device
- Other action taken due to this AE
- Time since last dosing and duration

Two AE listings will be presented, one including all AEs that occurred during the trial and one including only death, serious, other serious and other significant AEs (incl AEs that lead to discontinuation). The AE listing including all AEs does not contain AEs related to hypoglycemic events. These will be presented separately (see Section 5.10.2). AESIs (hepatic events) will be listed separately, if they will occur.

5.10.2 Analysis of Hypoglycaemic Events

Hypoglycaemic events will be presented for all subjects in the SFAS by individual listings, and summary tables.

The following summary tables of hypoglycaemic events will be presented:

- Hypoglycaemic events total and within each classification as given in Section 4.6, separated by type of the episode, outcome, treatment and treatment administration.
- Separate tables will be presented for severe and non-severe hypoglycaemic events, if there are more than two severe hypoglycaemic events (Level 3).
- All presentations will be done by treatment/visit.

The incidence of hypoglycaemic events will be presented with the number and percentage of participants affected. Percentages will be derived as ratio of number of participants affected and number of participants at risk multiplied by 100.

The following will be included in the overall listing of AEs related to hypoglycaemic events:

- Screening and randomisation number
- Gender, age, race and weight
- Event number
- Treatment/Visit
- Classification (Level 1-3,)
- Type of hypoglycaemic episode
- Nocturnal hypoglycaemia
- Start date and time
- End date and time
- Last dose date and time
- Time since last dosing and duration of the episode
- Lowest glucose level during the episode, if available (incl specimen)
- Outcome
- Treatment (incl time of treatment)
- Glucose level before treating the episode, if available (incl specimen)
- Treatment administration (self, capable self, not capable self)
- Other treatment actions

A separate listing of severe hypoglycaemic episodes (level 3) will be provided including narratives, giving qualitative descriptions of the severe episodes.

5.10.3 Analysis of Laboratory Safety Parameter

Laboratory safety variables (continuous values) will be summarised by descriptive statistics and by visit.

- Clinical chemistry, haematology: absolute and change from screening to follow-up

The reference range indicator (normal, low, high) per variable will be summarised by frequencies.

- Urinalysis: absolute and shifts from screening to follow-up

Summaries will be performed by visit. All laboratory values will be listed by visit and subject number including flagging of values outside normal range ("NCS": not clinically significant; "CS": clinically significant). A listing of abnormal values will be presented in an end of text (EOT) listing. In case of a re-screening of a subject, it will be discussed at the DBR meeting which values should be included in the summary table (i.e. values from the first screening or values from the re-screening). The decision and the reason will be stated in the DBR meeting minutes. A footnote will be added to the summary table.

5.10.4 Analysis of Electrocardiograms

ECG data will only be collected and listed. No analysis is planned.

5.10.5 Analysis of Vital Signs

Vital signs data (absolute and change from Day -1 to follow-up) will be presented by individual listings. In addition, summaries will be presented using descriptive statistics. Qualitative vital signs data will be summarised in a frequency table. Summaries will be separated by visit or treatment period; on treatment periods summaries will be done by treatment and day. In addition to the pre-specified assessments in protocol Section 2, BP and pulse may be assessed at any time during the trial at the discretion of the Investigator. All these values will be listed. A listing of abnormal values including flagging of values outside normal range ("NCS": not clinically significant; "CS": clinically significant) will also be presented.

5.10.6 Analysis of Physical Examinations

Abnormal physical examinations will be presented.

5.11 Analysis of Other Exploratory Parameters

All other exploratory parameters will be presented for all subjects in the FAS by individual listings, summary tables and figures. All figures will be presented on linear scale. Individual profiles will be presented including all available data. Mean profiles will be presented including all data used in the statistical analysis.

5.12 Analysis of Plasma Glucose for Safety

Individual listings of blood glucose for safety will be presented by treatment.

5.13 Analysis of Other Assessments

Concomitant medication data will be presented by individual listings. In addition, tabular summaries will be done.

Pregnancy test data, alcohol test and body weight will be presented by individual listings. In addition, tabular summaries will be done.

Carbohydrates at standard liquid meal (in detail: Total estimated carbohydrates for a complete meal are 63 g, Total estimated carbohydrates for a complete meal, Meal consumed completely? Non-consumed carbohydrate amount, Consumed amount of carbohydrates, Consumed amount of carbohydrates [%]) will be presented by individual listings. 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.In addition, tabular summaries will be done.

5.14 Subject Disposition

Disposition of subjects will be tabulated including:

- Number of Screened Subjects
- Number of Screening Failures
- Number of randomised subjects
- Number and percent of subjects exposed to LY900014 and Humalog®
- Number and percent of subjects exposed to LY900014 and Humalog® (infusion via pump/ Day 1)
- Number and percent of subjects exposed to LY900014 and Humalog® (injection via syringe/ Day 2)
- Number and percent of completers
- Number and percent of discontinued subjects
- Number and percent of subjects in each analysis set

The calculation of percent will be based on the number of randomised subjects. Subject disposition and observations excluded from analysis sets will be listed.

5.15 Treatment Compliance

Administered doses (basal rate and bolus) of IMPs will be listed and summarized by treatment and dosing day, including body weight and basal insulin suspension/ bolus administration.

5.16 Important Protocol Deviations

Important protocol deviations will be listed.

5.17 Screening Failures and Discontinuations

A listing of subjects who discontinued from the trial by reason for termination and a separate listing for all screening failures will be presented.

5.18 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.

6 ITEMS FOR STATISTICAL DOCUMENTATION

The statistical documentation to be included in an appendix to the CSR will include:

- SAP
- Relevant output from statistical analyses

7 SOFTWARE

Software used for randomisation, parameter calculation and statistical analysis are mentioned in the corresponding sections of the SAP. PK parameters, analysed by Eli Lilly, will use standard noncompartmental methods of analysis (Phoenix® version 6.3 or above).

8 REFERENCES

1. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials E9. International, Conference on Harmonisation E9 Expert Working Group. 1998.
2. ICH E3 Guideline for Industry. Structure and Content of Clinical Study Reports. July 1996
3. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes care. 2019;42(Suppl 1):S61-70.
4. Chow, S:C:; Liu, J.P. Design and Analysis of Bioavailability and Bioequivalence Studies, 3rd Ed.:Chapman and Hall/CRC, Taylor & Francis: New York: 2009

9 CHANGE IN STATISTICAL ANALYSIS FROM THE PROTOCOL

1. Protocol section 4.2.2 did not include all endpoints, which were named in protocol section 13.3.1. These endpoints have been added.

APPENDIX 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	
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 protocol section 8.9.2
[6] Re-check of dosing visit exclusion criteria.

APPENDIX 2 – ASSESSMENT SCHEDULE (FOR VISITS 2 AND 3)

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	
	B + 15min		X	X	
	B + 20min		X	X	
	B + 25min		X	X	

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other
	B + 30min	As soon as PG ≤ 140 mg/dL is measured, a confirmatory PG is performed	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)	
	B + 255min		X	X	
	(B + 260min)	If PG > 140 mg/dL		(X)	
	(B + 265min)	If PG > 140 mg/dL		(X)	

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose[1]	Other
	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.