Protocol I4L-MC-ABEF(c)

Relative Bioavailability of LY2963016 to LANTUS® After Single-Dose Subcutaneous Administration in Healthy Chinese Subjects

NCT03555305

Approval Date: 18-Dec-2018

1. Protocol I4L-MC-ABEF(c) Relative Bioavailability of LY2963016 to LANTUS® after Single-Dose Subcutaneous Administration in Healthy Chinese Subjects

LY2963016

This is a randomised, open-label, single-dose (0.5 U/kg), 2-treatment, 2-period, crossover study to compare the bioavailability of LY2963016 relative to that of LANTUS®.

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Protocol Electronically Signed and Approved by Lilly: 15 April 2013
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Protocol Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 18-Dec-2018 GMT

2. Synopsis

Clinical Pharmacology Protocol Synopsis: Study I4L-MC-ABEF

Name of Investigational Product: LY2963016	
Title of Study: Relative Bioavailability of LY2963016 to LANTUS® after Single-Dose Subcutaneous Administration in Healthy Chinese Subjects	
Number of Planned Subjects: Up to 60 subjects may be enrolled in order for 40 subjects to complete the study.	**Phase of Development:** 1
Length of Study: Approximately 1 month	
Objectives: **Primary:** To evaluate the relative bioavailability of LY2963016 compared to LANTUS following subcutaneous (SC) single-dose administrations (0.5 U/kg) in healthy Chinese subjects. **Secondary Objectives:** • To evaluate safety and tolerability of LY2963016 when administered to healthy Chinese subjects. • To compare other pharmacokinetic (PK) parameters of LY2963016 with those of LANTUS after 0.5-U/kg SC administration. • To compare the pharmacodynamic (PD) responses of LY2963016 with those of LANTUS after 0.5-U/kg SC administration.	
Study Design: This is a randomised, inpatient, open-label, single-dose (0.5 U/kg), 2-treatment, 2-period crossover euglycaemic clamp study to evaluate the relative bioavailability of LY2963016 to LANTUS.	
Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female, native healthy Chinese subjects aged 18 to 40 years, inclusive, with a body mass index between 18 and 28 kg/m^2 (inclusive), and who agree to use a reliable form of birth control during the study.	
Investigational Product, Dosage, and Mode of Administration: LY2963016 100-U/mL solution, as 0.5-U/kg dose, given SC once, alternating between the lower 2 quadrants of the abdominal wall, approximately 5 cm from the umbilicus.	
Comparator, Dose, and Mode of Administration: LANTUS 100-U/mL solution, as 0.5-U/kg dose, given SC once, alternating between the lower 2 quadrants of the abdominal wall, approximately 5 cm from the umbilicus.	
Planned Duration of Treatment: During each treatment period, subjects will receive a single dose of LY2963016 or LANTUS. Washout between the periods will be at least 7 days. Total study duration is approximately 1 month.	

Criteria for Evaluation:

Safety: Adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory tests, and medical assessments.

Bioanalytical: Blood glucose concentrations will be collected and analysed immediately from whole blood samples by an automated glucose oxidase technique or other appropriate analytical method. Human serum samples will be collected and analysed for serum insulin glargine or C-peptide concentrations by a validated method.

Pharmacokinetic/Pharmacodynamic: PK and PD parameters will be determined using noncompartmental methods of analysis. The primary PK parameters are area under the serum study drug concentration versus time curve (AUC) from zero to 24 hours [AUC(0-24)] and maximum serum study drug concentration (C_{max}). Secondary PK parameters include AUC from time zero to the last measurable time [AUC(0-t_{last})] and AUC from time zero to infinity [AUC(0-∞)], time to C_{max} (t_{max}), apparent clearance (CL/F), apparent terminal half-life ($t_{1/2}$), and the apparent volume of distribution (Vz/F). PD parameters include the maximum glucose infusion rate (R_{max}), total glucose infused during the clamp procedure (G_{tot}), time of R_{max} (tR_{max}).

Statistical Evaluation Methods:

Safety: Safety laboratory parameters, vital signs, ECG parameters, and AEs will be listed and summarised using standard descriptive statistics.

Statistical: The primary and secondary PK and PD parameters will be log-transformed prior to analysis. The model will include subject as a random effect, with period, sequence, and treatment as fixed effects. For each PK and PD parameter, the comparison will be evaluated as the ratio of the least-squares geometric means of test formulation (LY2963016) to reference formulation (LANTUS). The estimate of the ratio of means between the 2 treatments and the corresponding 90% confidence interval will be provided. Descriptive statistics will be reported for all PK and PD parameters.

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4. Abbreviations and Definitions

Term	Definition
adverse event (AE)	Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AUC	area under the serum study drug concentration versus time curve
AUC(0-∞)	area under the serum study drug concentration curve from time zero to infinity
AUC(0-24)	area under the serum study drug concentration-time curve from zero to 24 hours
AUC(0-t_{last})	area under the serum study drug concentration curve from time zero to last measured concentration value
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BMI	body mass index
case report form (CRF)	sometimes referred to as clinical report form: A printed form for recording study participants' data during a clinical study, as required by the protocol.
CI	confidence interval
CL/F	apparent systemic clearance
CLRM	Clinical Laboratory Results Modernization
C_{max}	maximum serum study drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug-delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.

consent	The act of obtaining informed consent for participation in a clinical trial from subjects deemed eligible or potentially eligible to participate in the clinical trial. Subjects entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.
CRO	contract research organisation: A person or organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of the sponsor's trial-related duties and functions.
CRU	clinical research unit
CSE	clinically significant event: A moderate to severe adverse event, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject.
ECG	electrocardiogram
end of study	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
enrol	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
ERB	ethical review board: A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical trial are protected.
GCP	good clinical practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
GIR	glucose infusion rate
G_{tot}	total amount of glucose infused
HIV	human immunodeficiency virus
IB	Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product that is relevant to the study of the investigational product in human subjects.
ICF	informed consent form: A Lilly term used to describe (1) information regarding the trial for the subject, and (2) the document that the subject signs to indicate consent to participate in the clinical trial
ICH	International Conference on Harmonisation
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

PD	pharmacodynamic(s)
PG	plasma glucose
PK	pharmacokinetic(s)
QD	once daily
R_{max}	maximum glucose infusion rate
SAE	serious adverse event: Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
$t_{1/2}$	apparent terminal half-life
t_{max}	time of maximum serum study drug concentration
TPO	third-party organisation
tR_{max}	time of maximum glucose infusion rate
Vz/F	apparent volume of distribution

Relative Bioavailability of LY2963016 to LANTUS® after Single-Dose Subcutaneous Administration in Healthy Chinese Subjects

5. Introduction

5.1. General Introduction

LY2963016 (Basaglar®) is a long-acting human insulin analogue, having the same primary amino acid sequence as LANTUS® (insulin glargine) and similar in qualitative and quantitative composition to LANTUS.

LANTUS is a recombinant human insulin analogue administered as a subcutaneous (SC) injection that is indicated for once-daily (QD) SC administration for the treatment of patients with diabetes mellitus for the control of hyperglycaemia (LANTUS package insert, 2015). Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine, and 2 arginines are added to the C-terminus of the B-chain. These structural modifications effectively shift the isoelectric point of the molecule, which decreases solubility of the insulin glargine at the physiologic pH of SC tissues. Upon injection of the insulin glargine solution into the SC tissue, the acidic solution is neutralised, microprecipitates form, and small amounts of insulin glargine are slowly released. This results in a relatively constant plasma concentration of insulin glargine over 24 hours with no pronounced peak.

In a 4-week repeat-dose toxicology study, rats were administered QD SC doses of 0, 0.3, 1.0, and 3.0/2.0 mg/kg of LY2963016 or LANTUS. The dose-limiting toxicity was severe hypoglycaemia for both LY2963016 and LANTUS; based on this, the no-observed-adverse-effect level, and maximum tolerated dose was 0.3 mg/kg for both LY2963016 and LANTUS. Findings common to insulin analogues, including neuropathy, lipohypertrophy, and islet cell atrophy, were produced in rats by LY2963016 and LANTUS at identical doses and were related to hyperinsulinaemia or hypoglycaemia. While the margins of safety for hypoglycaemia are moderate in rats (15.9-fold), this is not unusual in the development of insulin analogues.

Chemical and biological activity testing demonstrated the similarity of LY2963016 drug product to LANTUS. LY2963016 and LANTUS have comparable binding affinity to human insulin receptor, isoform A (IR-A), human insulin receptor, isoform B (IR-B), and human insulin-like growth factor 1 receptor (IGF-1R), highly similar in vitro functional activity, and highly similar in vitro mitogenic potential.

In 2 Phase 1 clinical studies, conducted in predominantly Caucasian healthy subjects, LY2963016 serum concentrations increased gradually following single SC doses of 0.5 U/kg, indicating a slow, prolonged absorption with median time to maximum serum study drug concentration (t_{max}) of 12 hours. The serum concentration-time profile was relatively flat and constant over 24 hours, with the geometric mean value for apparent terminal half-life ($t_{1/2}$) being approximately 10 hours.

The pharmacokinetic (PK) parameters area under the serum study drug concentration versus time curve (AUC) from zero to 24 hours (AUC[0-24]) and maximum serum concentration (C_{max}) of LY2963016, and the pharmacodynamic (PD) parameters total amount of glucose infused (G_{tot}) and maximum glucose infusion rate (GIR) (R_{max}) during a euglycaemic glucose clamp were similar to LANTUS and similar durations of action were observed.

Across 5 completed clinical pharmacology studies, conducted in predominantly Caucasian subjects, 209 healthy subjects received at least 1 dose of LY2963016 and 247 healthy subjects received at least 1 dose of LANTUS. When data were combined for all 5 studies, a total of 215 treatment-emergent adverse events (TEAEs; all causalities) were reported by 112 (53.6%) LY2963016-treated subjects and 327 TEAEs were reported by 149 (60.3%) LANTUS-treated subjects. The TEAEs that occurred in ≥5% of subjects with either treatment were: headache, procedural site reaction, catheter site swelling, catheter site pain, and catheter site hematoma. The TEAEs that were judged by the investigator to be related to study drug that occurred in ≥1% of subjects with either treatment were: injection site pain, injection site erythema, hypoglycaemia, vomiting, and headache. One clinical pharmacology study was conducted in 20 subjects with T1DM, each of whom received single doses of LY2963016 and LANTUS; a total of 9 TEAEs were reported by 5 subjects, none of which were considered to be related to study drug.

A total of 268 and 276 patients with T1DM and 376 and 380 patients with T2DM were randomized to receive at least 1 dose of LY2963016 or LANTUS, respectively, in the 2 Phase 3 clinical studies. During the 52-week study comparing efficacy and safety of LY2963016 and LANTUS in patients with T1DM, the incidence of TEAEs reported was similar among treatment groups; 167/268 (62.3%) of patients in the LY2963016 group and 166/267 (62.2%) of patients in the LANTUS group reported TEAEs. Overall, the most frequently reported TEAEs were: nasopharyngitis (experienced by 16.0% and 16.9% of patients treated with LY2963016 and LANTUS, respectively), upper respiratory tract infection (8.2% and 7.9% of patients, respectively), hypoglycaemia (4.9% and 4.5% of patients, respectively), and diarrhoea (4.5% and 3.7% of patients, respectively).

During the 24-week study comparing LY2963016 and LANTUS in patients with T2DM, 196/376 (52.1%) of patients in the LY2963016 group and 184/380 (48.4%) of patients in the LANTUS group reported TEAEs. Overall, the most frequently reported TEAEs were: nasopharyngitis (5.7%); upper respiratory tract infection (4.5%); and diarrhoea (3.0%).

More detailed information about the known benefits and risks of LANTUS and LY2963016 may be found in the package insert (LANTUS package insert, 2015) and LY2963016 Investigator's Brochure (IB) and package insert (Basaglar Package Insert 2015), respectively.

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP), International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.2. Rationale and Justification for the Study

This study is being conducted to support the submission of LY2963016 in China. LY2963016 is being developed as an insulin glargine similar to LANTUS. This study will evaluate the bioavailability and PD of LY2963016 relative to LANTUS after single 0.5-U/kg SC doses when administered to healthy Chinese subjects. This study is designed in accordance with requirements in the "Technical Guidance of Human Bioavailability and Bioequivalence Studies of Chemical Drugs" (China Food and Drug Administration [CFDA], 2005).

6. Objectives

6.1. Primary Objective

To evaluate the relative bioavailability of LY2963016 compared to LANTUS following SC single-dose administrations (0.5 U/kg) in healthy Chinese subjects.

6.2. Secondary Objectives

- To evaluate the safety and tolerability of LY2963016 when administered to healthy Chinese subjects.
- To compare other PK parameters of LY2963016 with those of LANTUS after 0.5-U/kg SC administration.
- To compare the PD responses of LY2963016 with those of LANTUS after 0.5-U/kg SC administration.

7. Investigational Plan

7.1. Summary of Study Design

This is a randomised, open-label, single-dose (0.5 U/kg), 2-treatment, 2-period, crossover, single-site, euglycaemic clamp study to evaluate the relative bioavailability of LY2963016 to LANTUS in healthy subjects. The study will have 2 treatment periods, with subjects randomly assigned in a 1:1 fashion to a treatment sequence of either LY2963016 (Period 1) followed by LANTUS (Period 2), or LANTUS (Period 1) followed by LY2963016 (Period 2) (Figure ABEF.7.1). Study drug will be administered once per period as an SC dose. Up to 60 healthy men and women will be enrolled in order to ensure that 40 subjects complete the study.

7.1.1. Screening Visit

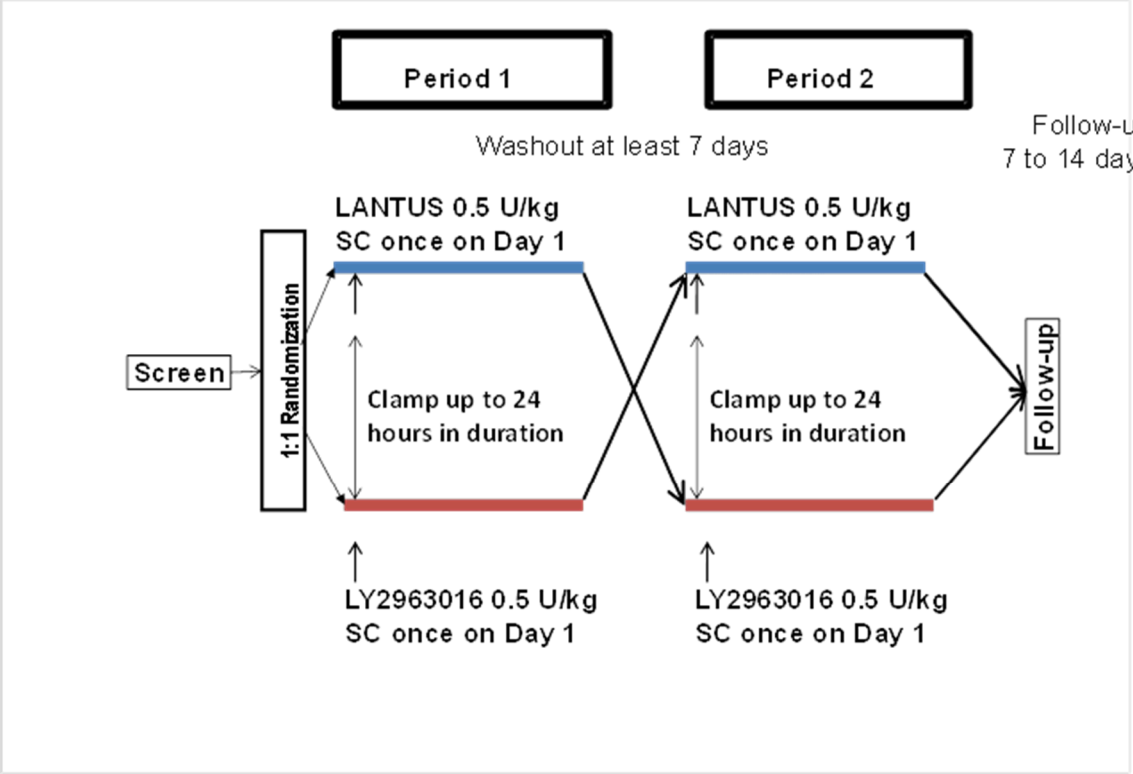
Subjects meeting all the inclusion criteria and none of the exclusion criteria may be enrolled into the study. The screening visit will occur within 4 weeks prior to enrolment (occurring on Period 1, Day -1).

7.1.2. Study Periods 1 and 2

Subjects will be admitted to the clinical research unit (CRU) on Day -1 of each period. On Period 1, Day -1, subjects will be randomly assigned in a 1:1 fashion to the treatment sequence of either LY2963016 followed by LANTUS or LANTUS followed by LY2963016. On Day -1 of each period, a clinical laboratory blood sample (local laboratory) will be collected in order to check for the subject's continued eligibility. Subjects who are no longer eligible will be withdrawn and replaced.

On Day 1 of each period, subjects will begin the preclamp procedure up to 120 minutes prior to dosing, and following dosing the euglycaemic clamp procedure will continue up to 24 hours. Blood samples will be collected over the 24-hour clamp procedure to determine serum concentrations of insulin glargine for PK evaluations; for blood glucose measurements for PD (see Section 10.1.3 for details of the clamp procedure), and for measurement of C-peptide. Following completion of the clamp procedure on Day 2, subjects will remain in the CRU until a post-clamp safety evaluation is performed. The interval between treatment administrations will be at least 7 days.

Safety will be assessed throughout the study by adverse event (AE) and concomitant medication monitoring, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), weight, and vital sign measurements. Protocol Attachment 1 presents a schedule of events for this study.



Abbreviation: SC = subcutaneous.

Figure ABEF.7.1. Study ABEF study design.

7.1.3. Follow-up Visit

In case of early discontinuation, subjects will return to the CRU between 7 and 14 days for a follow-up visit. Subjects who have completed the study should return between 7 and 14 days of the end of the last study period for the follow-up visit.

7.2. Discussion of Design and Control

An open-label design is appropriate because the study endpoints of PK and PD key parameters are not subject to bias. A single-dose euglycaemic clamp study design in healthy subjects is appropriate to evaluate the relative bioavailability of LANTUS to LY2963016. Lastly, the crossover design allows each subject to serve as his/her own control, thus reducing variability.

7.3. Determination of Sample Size

Up to 60 healthy subjects may be enrolled to ensure that at least 40 subjects complete the study. With 40 subjects completing, there is 80% coverage probability that the half-width of the 90% confidence interval (CI) of the difference of means for AUC will be within 0.223 in the log scale, which corresponds to approximately 20% in the ratio scale. This precision estimate was based on the intrasubject variability for AUC of 39.26% observed in completed studies in healthy

subjects. Drop-outs may be replaced and the replacement subject would assume the withdrawn subject's treatment sequence (receiving both allocated treatments).

8. Study Population

8.1. Criteria for Enrolment

Eligibility of subjects for study enrolment will be based on the results of a screening medical history, physical examination, clinical laboratory tests, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 4 weeks prior to enrolment.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened once. The interval between re-screenings should be at least 2 weeks. If re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

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

8.1.1. Inclusion Criteria

Subjects are eligible for enrolment in the study only if they meet **all** of the following criteria:

[1] Are native Chinese men or women. Native Chinese is defined as a subject who has both parents and all 4 grandparents of Chinese origin.

[2] Are overtly healthy males or females, as determined by medical history and physical examination.

[3a] For females of childbearing potential (defined as not surgically sterilised and between menarche and 1-year postmenopause) only:

- Negative serum pregnancy test at the time of screening.
- Are not lactating.
- Intend not to become pregnant during the study.
- Are sexually inactive or have practiced a reliable method of birth control (for example, use of oral contraceptives or levonorgestrel; diaphragms with contraceptive jelly; cervical caps with contraceptive jelly; condoms with contraceptive foam; intrauterine devices; partner with vasectomy; or abstinence) for at least 6 weeks prior to screening.
- Agree to continue to use a reliable method of birth control (as determined by the investigator) during the study.

[3b] For females not of childbearing potential, must be:

- Surgically sterile, defined as having had a hysterectomy or bilateral oophorectomy or tubal ligation, and/or

- Menopausal, defined as having had no menses for at least 1 year, or a plasma follicular stimulating hormone value of >40 mIU/mL and no menses for at least 6 months, unless the subject is taking hormone-replacement therapy.

[4] Are between the ages of 18 and 40 years, inclusive, at screening.

[5] Having fasting plasma glucose <110 mg/dL (<6.1 mmol/L) and 2-hour glucose level <140 mg/dL (<7.8 mmol/L) on the 75 g oral glucose tolerance test.

[6] Have a body mass index (BMI) between 18 and 28 kg/m^2, inclusive, at screening.

[7] Are nonsmokers, have not smoked for at least 6 months prior to entering the study, and agree not to smoke (cigars, cigarettes, or pipes) or use smokeless tobacco for the duration of the study.

[8] Have normal blood pressure and pulse rate at screening, as determined by the investigator.

[9] Have an ECG, at screening, considered as within normal limits by the investigator.

[10] Have clinical laboratory test results within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.

[11] Have venous access sufficient to allow for blood sampling as per the protocol.

[12] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[13] Have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

8.1.2. Exclusion Criteria

Subjects will be excluded from study enrolment if they meet **any** of the following criteria:

[14] Are investigator site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[15] Are Lilly or Boehringer Ingelheim employees.

[16] Have a history of first-degree relatives known to have diabetes mellitus.

[17] Are persons who have previously completed or withdrawn from this study.

[18] Are currently enrolled in, have completed or discontinued within the last 30 days from a clinical trial involving an investigational product; or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[19] Have known allergies to insulin glargine or its excipients, or related drugs, or heparin, or have a history of relevant allergic reactions of any origin.

[20] Have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study medication; or of interfering with the interpretation of data.

[21] Show evidence of current significant active neuropsychiatric disease.

[22] Show evidence of current use of known drugs of abuse or a history of use within the past year.

[23] Show evidence of human immunodeficiency virus infection (HIV) and/or positive human HIV antibodies.

[24] Have positive hepatitis B surface antigen.

[25] Have donated >400 mL of blood in the last 6 months or donated >100 mL within the last 30 days.

[26] Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption while resident in the CRU (1 unit = 12 ounces or 360 mL of beer; 5 ounces or 150 mL of wine; 1.5 ounces or 45 mL of distilled spirits).

[27] Intend to use: prescription medication or over-the-counter medication or Chinese traditional medicine within 14 days before dosing (apart from vitamin/mineral supplements, occasional paracetamol, thyroid replacement, or birth control methods). If this situation arises, an otherwise suitable subject may be included at the discretion of the investigator.

[28] Are persons determined by the investigator to be unsuitable for any other reason.

8.2. Discontinuation

8.2.1. Discontinuation of Subjects

If the Sponsor or investigator identifies a subject who did not meet enrolment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist/clinical research physician and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist/clinical research physician to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

Some possible reasons for early discontinuation of study participation:

- Enrolment in any other clinical trial involving an investigational product or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - the investigator/physician decides that the subject should be withdrawn from the study
- Subject Decision
    - the subject requests to be withdrawn from the study
- Sponsor Decision
    - the investigator or Lilly stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- Adverse Event
    - if a clinically significant event (CSE) occurs, the investigational product is to be discontinued and appropriate measures taken. Lilly or its designee should be alerted immediately. A CSE will be defined as a moderate to severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject. Refer to Section 10.3.

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

Discontinuation procedures are outlined in the Study Schedule (Attachment 1).

8.2.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for any reason consistent with applicable laws, regulations, and GCP.

8.2.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Rationale for Selection of Dose

A dose of 0.5 U/kg has been selected for this study as it was used in the previous studies that evaluated the similarity in the PK and PD properties between LY2963016 and LANTUS. This dose yields measurable serum immunoreactive LY2963016 and insulin glargine concentrations and evaluable PD data for the comparison between LY2963016 and LANTUS. Previous studies have shown this dose to be safe in healthy subjects.

9.2. Investigational Product Formulations

LY2963016 will be supplied as a 100-U/mL solution.

LANTUS is available as a 100-U/mL solution.

LY2963016 and LANTUS should be stored refrigerated at 2°C to 8°C and should not be allowed to freeze. Discard LY2963016 or LANTUS if product has been frozen. Both agents should be stored in a locked and secured location.

9.3. Investigational Product Administration

LY2963016 U-100 will be administered by the site as one 0.5-U/kg dose SC.

LANTUS U-100 will be administered by the site as one 0.5-U/kg dose SC.

All clinical trial material provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained.

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent(s) to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

The study insulin preparation to be injected during a given study period will be determined by a randomisation schedule. Where possible, the same site personnel will administer the study drug to the same subject on each dosing occasion.

The study insulin preparation will be allowed to come to approximately room temperature prior to injection. The qualified site personnel will be instructed on proper preparation, mixing, and administration techniques for all insulin used in this study. All insulin injections will be given by an appropriately qualified member of the CRU designated by the investigator. If possible the same individual should give the injection to the same subject for both administrations.

Doses used in each study period will be based upon subject's weight taken on Day-1 of Period 1. A calculated dose of n.00 to n.49 IU will be rounded down to n IU, whereas a calculated dose of n.50 IU to n.99 IU will be rounded up to n + 1 IU. The actual dose administered will be recorded on the case report form (CRF). All insulin injections will be given in the CRU subcutaneously. The appropriate needle will be applied at approximately 90 degrees into a raised skinfold to ensure consistent SC administration. The injection site shall be alternated between the lower 2 quadrants of the abdominal wall, approximately 5 cm from the umbilicus.

A dispensing record detailing the formulation and the amount received and dispensed will be kept by the CRU personnel. Unused medications will remain in the CRU until a determination has been made for their destruction.

Subjects will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational product so that the situation can be assessed.

For both periods, the doses will be administered at approximately the same time each morning on the dosing day. The actual time of dose administrations will be recorded in the subject's CRF.

9.4. Specific Restrictions/Requirements

Prior to beginning the study, the subjects will complete informed consent.

Throughout the study, subjects may be subject to medical assessment and review of compliance with restrictions before continuing in the study. Subjects should continue to meet the inclusion and exclusion criteria at the start of each study period, including restrictions related to contraception and medication use.

Dietary Restriction

Subjects will be fasted from approximately 8 hours prior to start of each clamp until after the glucose clamp procedure is completed. Water can be consumed freely during this time.

When at home, subjects will be encouraged to follow their normal diet.

Alcohol

No alcohol will be allowed at least 1 day prior to admission to the CRU and while resident in the CRU.

Sleep/Activity

Subjects are encouraged to maintain their regular exercise; however, they should not undertake vigorous or prolonged exercise at least 48 hours prior to each dosing day.

During the clamp procedure, subjects should remain recumbent or sitting in the CRU. Movement will be restricted to ensure subject safety and retain integrity of connections to infusion and study procedures.

Authorisation to leave the CRU must be given by a physician.

9.5. Blinding

This is an open-label study.

9.6. Concomitant Therapy

If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or clinical research physician. Any additional medication used during the course of the study must be documented.

Subjects should not use over-the-counter or prescription medication or Chinese traditional medicines within 14 days before dosing (apart from vitamin/mineral supplements, occasional paracetamol, thyroid replacement, or birth control methods). If a subject does use these medications, inclusion of the subject may be at the discretion of the investigator.

Subjects may not use traditional Chinese medicines during this study.

10. Pharmacokinetic, Pharmacodynamic, and Safety Data Collection

10.1. Pharmacokinetic and Pharmacodynamic Evaluations

10.1.1. Samples for Pharmacokinetic and Pharmacodynamic Measurements

During each clamp, venous blood collection (approximately 4 mL) for the determination of the serum concentrations of insulin glargine will begin prior to and continue for up to 24 hours after administration of LY2963016 or LANTUS. Samples (approximately 2.5 mL) will also be taken for the analysis of C-peptide concentrations. Timing of sample collection may be found in Attachment 1; an estimate of total blood volume to be collected during the study may be found in Attachment 3.

The timing of scheduled samples may be adjusted according to clinical needs. The actual collection times will be recorded. Blood samples will be collected via a venous cannula or direct venipuncture. Instructions for the collection and handling of blood samples will be provided by the sponsor. Serum will be obtained by centrifugation and stored at -20°C or below.

10.1.2. Bioanalysis

Serum samples will be analysed for concentrations of LY2963016 or LANTUS using a validated radioimmunoassay method. This insulin assay does not differentiate between LY2963016 or LANTUS and other insulins (endogenous or exogenous).

In addition, serum samples will be analysed for concentrations of C-peptide using a validated method.

Samples will be analysed at a laboratory approved by the sponsor. Instructions for the collection and handling of blood samples will be provided.

Bioanalytical samples collected to measure immunoreactive insulin glargine concentration only will be retained for a maximum of 2 years following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism.

10.1.3. Pharmacodynamic Evaluations (Glucose Clamp Procedure)

The aim of the euglycaemic glucose clamp is to maintain euglycaemia through glucose infusion after the administration of a dose of insulin. During the glucose clamp, the GIR will be adjusted to maintain a predetermined target blood glucose concentration for the individual subject. The intent is to maintain blood glucose concentrations approximately at the predose target value, which is defined as 5 mg/dL below the mean predose fasting blood glucose (mean of predose values recorded at approximately -30, -20, and -10 minutes).

Thus, blood glucose concentrations are kept constant while the GIR varies. The varying GIR will reflect the PD activity of insulin.

The subjects will participate in a total of 2 euglycaemic clamps on 2 separate study periods. Glucose clamp studies will be performed after an overnight fast of approximately 8 hours. The GIRs required to maintain euglycaemia and blood glucose concentrations will be documented throughout the procedure. On the morning of the study, a small catheter will be placed into a forearm vein, ideally at the elbow, for infusion of glucose. Another catheter will be placed at the wrist or back of the hand, or in the case of difficult venous access, in the forearm as close to the wrist as possible, for blood sampling. Blood samples will be obtained at the bedside for immediate determination of whole blood glucose concentrations using an automated glucose oxidase technique or other appropriate analytical method. The glucose is infused as a 20% dextrose solution.

The time of study insulin dosing will be defined as time zero. Following the dosing, in conjunction with frequent blood sampling for measurement of blood glucose, glucose will be infused intravenously at a variable rate in order to maintain euglycaemia for approximately 24 hours. If the GIR falls to zero for at least 30 minutes after the clamp has been underway for at least 8 hours, the clamp will be discontinued.

At the end of the clamp (approximately 24 hours after study drug administration) and following collection of the 24 hour study samples, the subject will be fed and medically assessed before discharge.

10.2. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry, haematology, and urinalysis panels, will be performed. For women of childbearing potential, a serum pregnancy test will be performed. Standard clinical laboratory tests for safety will be analysed by a central or local laboratory (see Attachment 1). Attachment 2 lists the specific tests that will be performed for this study. Attachment 3 summarises the blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Investigators must document their review of each safety laboratory report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.3. Safety Evaluations

10.3.1. Safety Measures

10.3.1.1. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Study Schedule and as clinically indicated (Attachment 1).

10.3.1.2. Vital Signs

Body temperature, blood pressure, and pulse rate will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1).

Additional vital signs may be measured during each study period if warranted and agreed upon between the sponsor and investigator.

10.3.1.3. Body Weight/Height

Body weight and height will be recorded as specified in the Study Schedule and as clinically indicated (Attachment 1). The screening weight will be used to satisfy the inclusion/exclusion criteria. The weight measured at Period 1 will be used for insulin glargine dosage calculation.

10.3.1.4. Electrocardiograms

For each subject, a 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1). Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed to ensure high-quality records.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

10.3.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

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.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational

product or the study, or that caused the subject to discontinue the investigational product before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the ICF is signed, study site personnel will record, via CRF, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Any clinically significant findings from ECGs, laboratory tests, vital sign measurements, other procedures, etc that result in a diagnosis should be reported to Lilly or its designee.

In addition, all AEs occurring after the subject receives the first dose of the investigational product must be reported to Lilly or its designee via electronic data entry.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, investigational product, and/or drug-delivery system via CRF.

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

10.3.2.1. Hypoglycaemia

Hypoglycaemia will be described using the following definitions:

Documented Glucose Alert Level (Level 1), plasma glucose (PG) ≤70 mg/dL (3.9 mmol/L)

- **Documented symptomatic hypoglycaemia:** with typical symptoms of hypoglycaemia.
- **Documented asymptomatic hypoglycaemia:** without typical symptoms of hypoglycaemia.
- **Documented unspecified hypoglycaemia**: with no information about symptoms of hypoglycaemia available. (This has also been called unclassifiable hypoglycaemia.)

Documented Clinically Significant Hypoglycaemia (Level 2) with similar criterion as above except for threshold PG <54 mg/dL (3.0 mmol/L)

- **Level 2 Documented symptomatic hypoglycaemia**
- **Level 2 Documented asymptomatic hypoglycaemia**
- **Level 2 Documented unspecified hypoglycaemia**

Severe hypoglycaemia (Level 3)

- **Severe hypoglycaemia:** Patients had 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 was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L]).

Other hypoglycaemia:

- **Nocturnal hypoglycaemia:** Any documented hypoglycaemic event (including severe hypoglycaemia) that occurs at night and presumably during sleep. This is captured as hypoglycaemia that occurs between bedtime and waking. This definition is more useful than the commonly used ~midnight to ~6 AM definition which does not take patients' individual sleep times into consideration, and is consistent with the ADA recommendations of reporting events that occur during sleep (ADA 2005). It is also important to collect the actual time when a hypoglycaemic event occurred to allow further characterization of hypoglycaemia timing (e.g., to allow analysis of frequency of events occurring across a 24-hr clock). Nocturnal hypoglycaemia may occur at severity Levels 1, 2, or 3.
- **Relative hypoglycaemia (also referred to as Pseudohypoglycaemia [Seaquist et al. 2013]):** An event during which typical symptoms of hypoglycaemia occur, that does not require the assistance of another person and is accompanied by PG >70 mg/dL (3.9 mmol/L). The PG value of patients with chronically poor glycaemic control can decrease so rapidly that patients may report symptoms of hypoglyacemia before their PG concentration falls below 70 mg/dL (3.9 mmol/L). Events with PG ≤70 mg/dL should not be categorized as relative hypoglycaemia. Evaluation and statistical analysis of this category is optional. However, if a patient reports a relative hypoglycaemia event where assistance from another person was received or the patient experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycaemia event, and report it appropriately.
- **Probable symptomatic hypoglycaemia:** Symptoms of hypoglycaemia were present, but PG measurement was not reported.

Only severe hypoglycaemic episodes will be reported separately as AEs. All episodes of severe hypoglycaemia will be reported as serious adverse events (SAEs).

The goal of the euglycaemic clamp is to maintain blood glucose concentrations at normoglycaemic levels close to a predefined target. Therefore, PG concentrations below 70 mg/dL (equivalent to blood glucose of approximately 63 mg/dL) will not routinely be recorded as hypoglycaemic events during the glucose clamp procedure. However, at the discretion of the investigator, a decrease in glucose concentrations may be recorded as a hypoglycaemic event based on clinical concern, or related to technical issues resulting in hypoglycaemia.

10.3.3. Serious Adverse Events

An SAE is any AE from this study that results in one of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.
- important medical events that may not be immediately life-threatening or result in death or require hospitalization but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.
- when a condition related to the investigational device necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Study site personnel must alert the Lilly clinical pharmacologist/clinical research physician, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the CRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the subject summary CRF has been completed). 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 the study treatment or study participation, the investigator must promptly notify Lilly.

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

10.3.4. Safety Monitoring

The Lilly clinical pharmacologist or clinical research physician will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or research physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist when appropriate, and will periodically review:

- trends in safety data,
- laboratory analytes, and
- AEs.

10.3.5. 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.

Complaints related to comparator drugs or concomitant drugs/drug-delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Appropriateness and Consistency of Measurements

All assessments made in this study are standard, widely used, and generally recognised as reliable, accurate, and relevant.

10.5. Compliance

Every attempt will be made to select subjects who have the ability to understand and comply with instructions. Noncompliant subjects may be discontinued from the study. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the study site.

The specifications in this protocol for the timings of safety, PK, and PD sampling are given as targets, to be achieved within reasonable limits. Modifications may be made to the time points

based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

Any major modifications that might affect the conduct of the study, subject safety, and/or data integrity will be detailed in a protocol amendment.

11. Data Management Methods

11.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives may periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

11.2. Data Capture Systems

11.2.1. Case Report Form

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

For data handled by a data management third-party organisation (TPO), CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the sponsor.

For data handled internally, CRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

11.2.2. Ancillary Data

Central laboratory data will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the contract laboratory to the Lilly Clinical Laboratory Results Modernization (CLRM) system and/or TPO's system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly CLRM system and TPO's system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Pharmacokinetic, Pharmacodynamic, and Safety Data Analyses

12.1. Data Analysis Plans

12.1.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or designee.

PK and PD analyses will be conducted on the full analysis set. This set includes all data from all subjects randomly assigned to a treatment sequence who receive at least 1 dose of study drug (according to the treatment actually received), and who have evaluable data. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.1.2. Study Participant Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

12.1.3. Study Participant Characteristics

The subject's age, sex, weight, height, or other demographic characteristics will be recorded.

12.1.4. Pharmacokinetic Analyses

12.1.4.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY2963016 and LANTUS will be calculated by standard noncompartmental methods of analysis. PK analyses will be conducted on those subjects with evaluable data.

The analyses will be performed according to the Lilly Global Pharmacokinetics, Pharmacodynamics, and Trial Simulation Divisional Standards. For each profile, concentration values that are below the quantifiable limit of the assay will be treated as missing data. Actual sampling times in individual subjects will be used in the analysis. The serum concentration of immunoreactive LY2963016 and LANTUS will be corrected for endogenous insulin using the C-peptide data. The primary parameters for PK analysis will be: AUC(0-24) and C_{max}. Other PK parameters that will be reported include: AUC from time zero to last measured concentration value [AUC(0-t_{last})], AUC from time zero to infinity [AUC(0-∞)], t_{max}, apparent clearance (CL/F), $t_{1/2}$, and the apparent volume of distribution (Vz/F). The AUC values will be calculated by the linear/log trapezoidal method, where the linear trapezoidal method will be employed up to t_{max}, and the log trapezoidal rule will be used for concentrations beyond t_{max}.

12.1.4.2. Pharmacokinetic Statistical Inference

The primary PK parameters, AUC(0-24) and C_{max}, will be log-transformed prior to analysis. A linear mixed effects model will be fitted to the data. The model will include subject as a random effect, with period, sequence, and treatment as fixed effects. For each PK parameter, the comparison will be evaluated as the ratio of the least-squares geometric means of LY2963016 to LANTUS. The estimate of the ratio of geometric means between the 2 treatments and the corresponding 90% CI will be provided. A similar statistical analysis may be performed for the log-transformed secondary PK parameters AUC(0-∞) and AUC(0-t_{last}). A nonparametric approach will be taken to evaluate t_{max}. Descriptive statistics may be reported for other PK parameters as deemed appropriate (eg, CL/F, Vz/F, $t_{1/2}$).

Exploratory analyses may be performed for other PK parameters as deemed appropriate.

12.1.5. Pharmacodynamic Analyses

12.1.5.1. Pharmacodynamic Parameter Estimation

The GIRs and blood glucose values will be recorded on Day 1. Glucose infusion rates will be used to calculate several PD parameters, including R_{max}, time of R_{max} (tR_{max}), and G_{tot}. Other parameters may be calculated as appropriate. The PD parameters will be calculated using S-PLUS® software (v8.2).

12.1.5.2. Pharmacodynamic Statistical Inference

The PD parameters (R_{max} and G_{tot}) will be log-transformed prior to analysis. A linear mixed effects model will be fitted to the data. The model will include subject as a random effect, with period, sequence, and treatment as fixed effects. From the models, the difference in least-squares mean estimates between the 2 treatments and the corresponding 90% CIs for the difference will be estimated and back-transformed from the log scale to provide estimates of the ratios of geometric means and 90% CI for the ratio of these means. A nonparametric approach will be taken to evaluate tR_{max}.

Exploratory analyses of the PD time parameters may be performed as deemed appropriate.

12.1.6. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

12.1.7. Safety Analyses

12.1.7.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarised using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to study enrolment will be distinguished from those reported as new or increased in severity

during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

12.1.7.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECGs. The parameters will be listed, and summarised using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

12.2. Interim Analyses

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

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing any new information that may be relevant to the subject's willingness to continue his or her participation in the trial in a timely manner.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each subject before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of the investigational product.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study,
- ICF, and
- relevant curricula vitae.

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines,

2) the ICH GCP Guideline [E6], and

3) applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

All or some of the obligations of the sponsor will be assigned to a contract research organisation (CRO).

An identification code assigned by the investigator to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14. References

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Attachment 1. Protocol ABEF Study Schedule

Study Schedule Protocol I4L-MC-ABEF

Procedure	Screen[a]	Euglycaemic Clamp Procedure Periods 1 and 2[b]				Discharge
	Within 4 weeks prior to Day -1	Day -1 Pre-Clamp	Day 1 Pre-Clamp	Begin Day 1, End on Day 2	Day 2 Post-Clamp	Between 7 and 14 Days of End of Period 2 or Early Discontinuation
Informed consent	X					
Medical history	X					
Height	X					
Serum pregnancy test	X	X[c]				X
Urine ethanol and drug screen	X					
Hepatitis B and HIV test	X					
FSH (if applicable)	X					
OGTT	X					
ECG	X		X		X	X
Randomization		Period 1				
Physical examination	X		X[d]		X[d]	X
Vital signs[e] (supine)	X		X		X	X
Clinical laboratory tests[f]	X	X				X
Subject admission to CRU		X				
Weight	X	X[g]				
Glucose clamp procedures				X[h]		
Blood sampling for PK[i]				-0.5 (predose), 0 (predose), 0.5, 1, 2, 3, 4, 6, 9, 12, 15, 18, 21 hr	24 hr	
C-peptide sampling[i]				-0.5 (predose), 0 (predose), 0.5, 1, 2, 3, 4, 6, 9, 12, 15, 18, 21 hr	24 hr	
LANTUS or LY2963016 administration (0.5 U/kg single dose SC)				X		
Subject Discharge from CRU					X	

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; hr = hour(s); PK = pharmacokinetics; SC = subcutaneous; OGTT = oral glucose tolerance test.

a Subjects who are not enrolled within 4 weeks of screening may be subjected to additional medical assessments and clinical laboratory tests prior to study entry.

b The interval between treatment administrations (washout) will be at least 7 days.

c Women of childbearing potential must have a negative serum pregnancy test ≤3 days prior to Day 1 of each period.

d Abbreviated physical examinations may be performed pre- and post-clamp at each period.

e Vital signs of supine pulse rate and supine blood pressure will be routinely measured. Body temperature will be measured on Day 1 of each period. During the clamp procedure, supine blood pressure and/or pulse rate may be measured as clinically indicated. Additional vital signs may be measured during each study visit, if warranted and agreed upon between Lilly and the investigator.

f Screening and follow-up clinical laboratory tests to be performed at a central laboratory. On Day -1 of each period, clinical laboratory sample should be collected and sent to a local laboratory and results should be reviewed to check subject's eligibility before dosing. See Attachment 2 for list of clinical laboratory tests performed.

g Weight will be recorded for all periods. Weight recorded at the first period only will be used for dose calculation, and the subjects will receive the same exact dose at each period.

h Blood sampling will occur per institutional procedures, but approximately every 10 minutes for approximately 30 minutes prior to dosing, and will continue approximately every 5 to 10 minutes for the first 2 hours after dosing, and may be reduced to 10- to 30-minute intervals up to the end of clamp. Repeat samples for spurious results or safety management may be taken where indicated.

i Sampling times are relative to the time of study drug administration.

Attachment 2. Protocol ABEF Clinical Laboratory Tests

Laboratory Tests

Haematology[a]:	Clinical Chemistry[a]:
Haematocrit	Sodium
Haemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume (MCV)	Chloride
Mean cell haemoglobin (MCH)	Calcium
Mean cell haemoglobin concentration (MCHC)	Phosphorus
Leukocytes (WBC)	Glucose (fasting)
Absolute counts of:	Blood urea
Neutrophils	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
Platelets	Alkaline phosphatase
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
Urinalysis[a]:	Creatinine
Specific gravity	Gamma-glutamyl transferase (GGT)
pH	
Protein	
Glucose	Serum pregnancy test (women of childbearing potential)[a]
Ketones	Hepatitis B surface antigen[b]
Bilirubin	HIV[c]
Urobilinogen	OGTT [b]
Blood	FSH (if applicable)[b]
	Urine ethanol testing[b]
	Urine drug screen[b]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OGTT = oral glucose tolerance test; RBC = red blood cells; WBC = white blood cells.

[a] Performed at screening and follow-up at a central laboratory and at a local laboratory on Day -1 of each Period.

[b] Performed at screening only at a central laboratory.

[c] Performed at screening only at a local laboratory.

Attachment 3. Protocol ABEF Blood Sampling Summary

This table summarises the maximum number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but these will not require a protocol amendment.

Purpose	Maximum Blood Volume per Sample	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening clinical laboratory tests[a]	30 mL	1	30
Central laboratory follow-up clinical laboratory tests	7.5 mL	1	7.5
Local laboratory clinical laboratory tests (Day -1 of each period)	7 mL	2	14
PK samples	4 mL	14 samples/clamp x 2 clamps	112
C-peptide samples	2.5 mL	14 samples/clamp x 2 clamps	70
Glucose clamp samples[a,b]	0.3 mL	27 hours/clamp x 2 clamps (approx. 159 samples/clamp)	95.4
Blood discard for cannula patency	0.2 mL/discard x 2 discards/hour	27 hours/clamp x 2 clamps	21.6
Total for study	-	-	approximately 351

[a] Additional samples may be drawn if needed for safety purposes.

[b] Blood sampling will occur per institutional procedures, but approximately every 10 minutes for approximately 30 minutes prior to dosing, and will continue approximately every 5 to 10 minutes for the first 2 hours after dosing, and may be reduced to 10- to 30-minute intervals up to the end of clamp.

Attachment 4. Protocol Amendment I4L-MC-ABEF(c) Summary Relative Bioavailability of LY2963016 to LANTUS® after Single-Dose Subcutaneous Administration in Healthy Chinese Subjects

Overview

Protocol I4L-MC-ABEF(b) [Relative Bioavailability of LY2963016 to LANTUS® after Single-Dose Subcutaneous Administration in Healthy Chinese Subjects] has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The change and rationale for the change made to this protocol are as follows:

- Human Immunodeficiency Virus (HIV) testing will now be performed at a local laboratory instead of a central laboratory.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Attachment 2. Protocol ABEF Clinical Laboratory Tests

Laboratory Tests

Haematology[a]:	Clinical Chemistry[a]:
Haematocrit	Sodium
Haemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume (MCV)	Chloride
Mean cell haemoglobin (MCH)	Calcium
Mean cell haemoglobin concentration (MCHC)	Phosphorus
Leukocytes (WBC)	Glucose (fasting)
Absolute counts of:	Blood urea
Neutrophils	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
Platelets	Alkaline phosphatase
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
Urinalysis[a]:	Creatinine
Specific gravity	Gamma-glutamyl transferase (GGT)
pH	
Protein	
Glucose	Serum pregnancy test (women of childbearing potential)[a]
Ketones	Hepatitis B surface antigen[b]
Bilirubin	HIV[~~b~~c]
Urobilinogen	OGTT [b]
Blood	FSH (if applicable)[b]
	Urine ethanol testing[b]
	Urine drug screen[b]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OGTT = oral glucose tolerance test; RBC = red blood cells; WBC = white blood cells.

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