Protocol I4L-GH-ABET (a)

A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to Lantus® in Adult Chinese Patients with Type 2 Diabetes Mellitus

NCT03338010

Approval Date: 2-Mar-2017

1. Protocol I4L-GH-ABET(a)
A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to Lantus® in Adult Chinese Patients with Type 2 Diabetes Mellitus

Confidential Information

LY2963016

Phase 3, randomized, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study with a 4-week post-treatment follow-up to compare LY2963016 and Lantus® in adult Chinese patients with type 2 diabetes mellitus.

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Protocol Electronically Signed and Approved by Lilly: 02 August 2016
Amendment (a) Electronically Signed and Approved by Lilly
on date provided below.

Approval Date: 02-Mar-2017 GMT

2. Synopsis

Study Rationale

LY2963016 is a highly similar version of Lantus® (insulin glargine [recombinant deoxyribonucleic acid (rDNA) origin] injection), the reference medicinal product (also referred to as the innovator product) produced by Sanofi-Aventis (Lantus® is a registered trademark of Sanofi-Aventis). The primary amino acid sequence of LY2963016 is the same as that of the active ingredient in Lantus®. Both LY2963016 and Lantus® have similar formulations. The present study is a randomized, open-label trial that will compare the efficacy and safety of LY2963016 to Lantus® in adult Chinese patients with type 2 diabetes mellitus (T2DM). The study patients will be insulin naïve and on 2 or more oral antihyperglycemic medications (OAMs) with inadequate glycemic control.

Clinical Protocol Synopsis: Study I4L-GH-ABET

Name of Investigational Product:
LY2963016

Title of Study: A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to Lantus® in Adult Chinese Patients with Type 2 Diabetes Mellitus

Number of Planned Patients/Subjects:	**Phase of Development:** Phase 3
Entered: 605 Enrolled/Randomized: 530 Completed: 450	

Length of Study:
Estimated first patient visit: Mar 2018 Estimated last patient visit: Feb 2020

Objectives: The primary objective of this study is to test the hypothesis that LY2963016 administered once daily (QD) is noninferior to Lantus® (QD) by a 0.40% margin, as measured by change in hemoglobin A1c (HbA1c) from baseline to 24 weeks, when used in combination with OAMs.

The secondary objectives of the study are:

- To test the hypothesis that Lantus® is noninferior to LY2963016 (QD), as measured by change in HbA1c from baseline to 24 weeks, when used in combination with OAMs. (this secondary objective is tested with a gated approach).
- To compare safety of LY2963016 relative to Lantus® (proportion of patients with detectable anti-glargine antibodies, hypoglycemia, and injection site reaction) when used in combination with OAMs.
- To compare change in HbA1c at 4, 8, 12, 16, and 20 weeks between LY2963016 and Lantus® when used in combination with OAMs.
- To compare 7-point self-monitored blood glucose (SMBG) profiles (as plasma equivalent values) at 0, 2, 6, 12, and 24 weeks between LY2963016 and Lantus® when used in combination with OAMs.
- To compare percentage of patients with HbA1c <7% and percentage of patients with HbA1c ≤6.5% at 4, 8, 12, 16, 20, and 24 weeks between LY2963016 and Lantus® when used in combination with OAMs.
- To compare LY2963016 to Lantus® when used in combination with OAMs with regard to the following measures:
  - intrapatient blood glucose (BG) variability
  - basal insulin dose
  - Weight
- To compare LY2963016 relative to Lantus® for patient-reported outcomes (PRO) as measured by responses to the Insulin Treatment Satisfaction Questionnaire (ITSQ).

Study Design: A Phase 3, prospective, randomized multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment and 4-week post-treatment follow-up study in adult Chinese patients with T2DM. The study patients will be insulin naïve and on 2 or more OAMs with inadequate glycemic control.

Diagnosis and Main Criteria for Inclusion and Exclusions:
Patients with T2DM aged ≥18 with a body mass index (BMI) ≤35 kg/m^2, on 2 or more OAMs at stable doses for at least 12 weeks prior to Visit 1 and with HbA1c ≥7.0% and ≤11.0%, will be included in the study.
Patients with significant liver, cardiac, or gastrointestinal disease will be excluded. Patients with active cancer or cancer within the previous 5 years (with the exception of basal cell carcinoma or carcinoma in situ) will be excluded. Patients with hypersensitivity to Lantus® or its excipients will be excluded.

Investigational Product, Dosage, and Mode of Administration or Intervention:
Patients will initiate treatment with a starting dose of 10 units (U) LY2963016 QD and will then be supervised by investigators through the course of the study to maintain the fasting blood glucose (FBG) ≤100 mg/dL (5.6 mmol/L) while avoiding hypoglycemia. The mode of administration will be subcutaneous.

Planned Duration of Treatment:
Lead-in period: None
Treatment period: 24 weeks
Washout period: None
Observation period: 4 weeks

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention:
Patients will initiate treatment with a starting dose of 10 U of Lantus® QD and will then be supervised by investigators through the course of the study to maintain the FBG ≤100 mg/dL (5.6 mmol/L) while avoiding hypoglycemia. The mode of administration will be subcutaneous.

Criteria for Evaluation:
Efficacy
Primary Endpoint:
Change in HbA1c from baseline to 24 weeks.
Secondary Endpoints:

- Change in HbA1c from baseline to 4, 8, 12, 16, and 20 weeks or last post-baseline observation carried forward (LOCF)
- Percentage of patients with HbA1c <7%; percentage of patients with HbA1c ≤6.5%
- 7-point SMBG (expressed as plasma-equivalent glucose values obtained before each meal; after each meal; at bedtime)
- Intrapatient variability as measured by the standard deviation (SD) of the 7-point SMBG
- Basal insulin dose in total units per day and daily units per kilogram
- Weight change
- Patient-reported outcomes as reflected in responses to ITSQ

Safety:
Anti-glargine antibodies, laboratory measurements, adverse events (AEs), serious adverse events (SAEs), and hypoglycemia will be evaluated for safety. Episodes of severe hypoglycemia will be captured as SAEs. Certain outcomes, such as death, early discontinuation because of AE, and investigator decision to discontinue a subject will also be evaluated for safety. Patients will report hypoglycemia, which is defined as an event associated with signs or symptoms consistent with hypoglycemia or a blood level of ≤70 mg/dL (≤3.9 mmol/L), even if it is not associated with signs or symptoms.
Injection-site reactions and neoplasms will be captured as AEs.
Health Outcomes:
Patient-reported outcomes as reflected in responses to ITSQ. The ITSQ is a validated instrument containing 22 items that assesses treatment satisfaction for persons with diabetes who are taking insulin.

Statistical Methods:

Sample Size:

Based on the primary objective, to show noninferiority of LY2963016 to Lantus® at the 0.40% noninferiority margin (NIM), 450 completers in total with a ratio 2:1 (LY2963016 versus Lantus®) are needed at 24 weeks. This calculation assumes no treatment difference in HbA1c between LY2963016 and Lantus®, common SD of 1.3% for change from baseline in HbA1c, 0.05 two-sided significance level, and over 85% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients is 530 in total (353 for LY2963016 and 177 for Lantus®).

Statistical:

The primary efficacy outcome will be the change in HbA1c level from baseline to 24 weeks. The primary analysis will be a likelihood-based, mixed model repeated measure (MMRM) approach, treating the data as missing at random (MAR) for the full analysis set (FAS) population. The MMRM model will evaluate the change from baseline in HbA1c level as the dependent variable with treatment (LY2963016, Lantus®), entry use of insulin secretagogues (sulfonylurea [SU], meglitinide, neither) , visit, and interaction between visit and treatment as fixed effects; the baseline value of HbA1c as a covariate; and a random effect for patient. Supportive analyses will be performed using the same MMRM model on per-protocol (PP) population and using an analysis of covariance (ANCOVA) model on FAS population.

The analysis of the continuous secondary efficacy and safety measurements will use the same MMRM model for the primary efficacy analyses with the baseline value of the response as a covariate with the FAS patient population. Continuous laboratory measures will be analyzed using an ANCOVA model. For categorical measures, Fisher's exact test or Pearson's Chi-square test will be used.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
ADA	American Diabetes Association
ACS	American Cancer Society
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable 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.
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
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, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BG	blood glucose
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock.
BMI	body mass index
case report form (CRF) and electronic case report form (eCRF)	Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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.
consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.

CRO	contract research organization
CRP (clinical research physician)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
ED	early discontinuation
ECG	electrocardiogram
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
end of study (trial)	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.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
FAS	full analysis set
FBG	fasting blood glucose
GCP	good clinical practice
GLP	glucagon-like peptide
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
Intent(ion) to treat (ITT)	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of

	treatment.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITSQ	Insulin Treatment Satisfaction Questionnaire
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
LOCF	last-observation-carried-forward or last post-baseline observation carried forward
LSMean	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measure
NIM	noninferiority margin
NPH	neutral protamine hagedorn
OAM	oral antihyperglycemic medication
OM	observed margins
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PG	plasma glucose
PP	per-protocol
PRO/ePRO	(electronic) patient-reported outcomes
QD	once daily
randomize	The act of assigning a patient to a treatment. Patients who are enrolled/ randomized in the trial are those who have been assigned to a treatment.

rDNA	recombinant deoxyribonucleic acid
SAE	serious adverse event
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 study.
SD	standard deviation
SMBG	self-monitored blood glucose or self-monitoring of blood glucose
Study entry	patients will be considered to have been entered into the study after they have signed the inform consent form
SU	sulfonylurea
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.
suspected unexpected serious adverse reactions (SUSARs)	Suspected unexpected serious adverse reactions are serious events that are not listed in the Investigator's Brochure (IB) and that the investigator identifies as related to investigational product or procedure.
T2DM	type 2 diabetes mellitus
TEAR	treatment emergent antibody response
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
U	unit(s)
ULN	upper limit of normal
WHO	World Health Organization

A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to Lantus® in Adult Chinese Patients with Type 2 Diabetes Mellitus

5. Introduction

Medical therapy, in the majority of patients with type 2 diabetes mellitus (T2DM), must be advanced over the course of the disease in order to maintain optimal glycemic control. As the disease progresses, beta-cell function deteriorates, often requiring individuals to add insulin to their medication regimen. A consensus algorithm jointly written by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes recommends insulin to be started with a single injection of intermediate or long-acting insulin at bedtime, or morning long-acting insulin (Nathan et al. 2009). Several clinical trials have demonstrated similar overall glycemic control between Lantus® (insulin glargine [recombinant deoxyribonucleic acid (rDNA) origin]; [Sanofi - Aventis, Bridgewater, New Jersey, USA]) and human insulin isophane suspension (NPH), but with a lower risk of hypoglycemia with Lantus® (Yki-Järvinen et al. 2000, 2006; Riddle et al. 2003; Rosenstock et al. 2005). Available data demonstrating Lantus®'s efficacy and enhanced safety profile, combined with its 24-hour duration of action, has made it the treatment of choice for health providers to enable patients with T2DM to achieve their clinical goals (Mathieu and Robbrecht 2008).

Lantus® differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. These changes shift the isoelectric point, producing a solution that is completely soluble at pH 4.0. When injected into the subcutaneous tissue, the acidic solution is neutralized (Pieber et al. 2000). This leads to the formation of microprecipitates, from which small amounts of insulin glargine are released. The slow dissolution of hexamers into dimers and, finally, monomers results in an extended duration of action without a pronounced peak (Lantus® US package insert, 2010).

LY2963016 is a highly similar version of Lantus® (insulin glargine [rDNA origin] injection), the reference medicinal product (also referred to as the innovator product) produced by Sanofi-Aventis (Lantus® is a registered trademark of Sanofi-Aventis). The primary amino acid sequence of LY2963016 is the same as that of the active ingredient in Lantus®. Both LY2963016 and Lantus® have similar formulations. The clinical development program for LY2963016 has generated evidence substantiating the similar nature in terms of clinical pharmacokinetics and pharmacodynamics, safety, and efficacy of LY2963016 and Lantus®. Study I4L-MC-ABEC was a phase 3, double-blind, 24-week trial to compare the efficacy and safety of LY2963016 to Lantus® in patients with T2DM. The study demonstrated LY2963016 was noninferior to Lantus®. Lantus® was also noninferior to LY2963016. Thus, LY2963016 and Lantus® were considered to have equivalent efficacy. Severe hypoglycemia was the most frequently reported serious adverse event (SAE; LY2963016: 2 patients [0.5%]; Lantus®: 3 patients [0.8%]). There were no statistically significant differences between treatment groups for the overall incidence and overall rate of each category/subcategory of hypoglycemia. There

were no statistically significant differences between treatment groups for the incidence of treatment-emergent adverse events (TEAEs) at the preferred term level. There were no statistically significant treatment differences for the proportion of patients with detectable insulin antibodies (post-hoc analysis) at endpoint (last-observation-carried-forward or last post-baseline observation carried forward [LOCF]) or overall, or for the proportion of patients that developed a treatment emergent antibody response (TEAR) at endpoint (LOCF) or overall. The safety profiles for LY2963016 and Lantus® were similar; there were no new safety findings in either treatment group. The data from this trial demonstrate that LY2963016 provides a well- tolerated and effective once daily (QD) basal insulin option for treatment of patients with T2DM in combination with oral antihyperglycemic medications (OAMs), with an efficacy and safety profile similar to that of Lantus® (insulin glargine).

The present study is a randomized, open-label trial that will compare the efficacy and safety of LY2963016 to Lantus® in Chinese patients with T2DM on 2 or more OAMs and with inadequate glycemic control (without insulin) at study entry. This study will expand the evaluation of the efficacy and safety of LY2963016 to a broader race/ethnic spectrum of patients with T2DM considering that the study population in Study ABEC was white (78.4%) and Asian (8.5%).

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.

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) of LY2963016 may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to test the hypothesis that LY2963016 administered QD is noninferior to Lantus® administered QD by a margin of 0.40%, as measured by change in hemoglobin A1c (HbA1c) from baseline to 24 weeks, when used in combination with OAMs.

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To test the hypothesis that Lantus® is noninferior to LY2963016 (QD), as measured by change in HbA1c from baseline to 24 weeks, when used in combination with OAMs. (this secondary objective is tested with a gated approach).
- To compare safety of LY2963016 relative to Lantus® (proportion of patients with detectable anti-glargine antibodies, hypoglycemia, and injection site reaction) when used in combination with OAMs.
- To compare change in HbA1c at 4, 8, 12, 16, and 20 weeks between LY2963016 and Lantus® when used in combination with OAMs.
- To compare 7-point self-monitored blood glucose (SMBG) profiles (as plasma equivalent values) at 0, 2, 6, 12, and 24 weeks between LY2963016 and Lantus® when used in combination with OAMs.
- To compare percentage of patients with HbA1c <7% and percentage of patients with HbA1c ≤6.5% at 4, 8, 12, 16, 20, and 24 weeks between LY2963016 and Lantus® when used in combination with OAMs.
- To compare LY2963016 to Lantus® when used in combination with OAMs with regard to the following measures:
    - intrapatient blood glucose (BG) variability
    - basal insulin dose
    - weight change
- To compare LY2963016 relative to Lantus® for patient-reported outcomes (PRO) as measured by responses to the Insulin Treatment Satisfaction Questionnaire (ITSQ).

7. Investigational Plan

7.1. Summary of Study Design

Study I4L-GH-ABET (ABET) is a Phase 3, prospective, randomized, multicenter, 2-arm, active control, open-label, parallel-design, 24-week study with a 4-week post-treatment follow-up. The study will compare 2 long-acting basal insulin analogs (LY2963016 and Lantus®) in patients with T2DM who are insulin naïve and have failed to achieve adequate glycemic control on at least 2 OAMs. This study is designed to determine noninferiority of LY2963016 to Lantus® in change in HbA1c from baseline when used to initiate insulin therapy in this patient population.

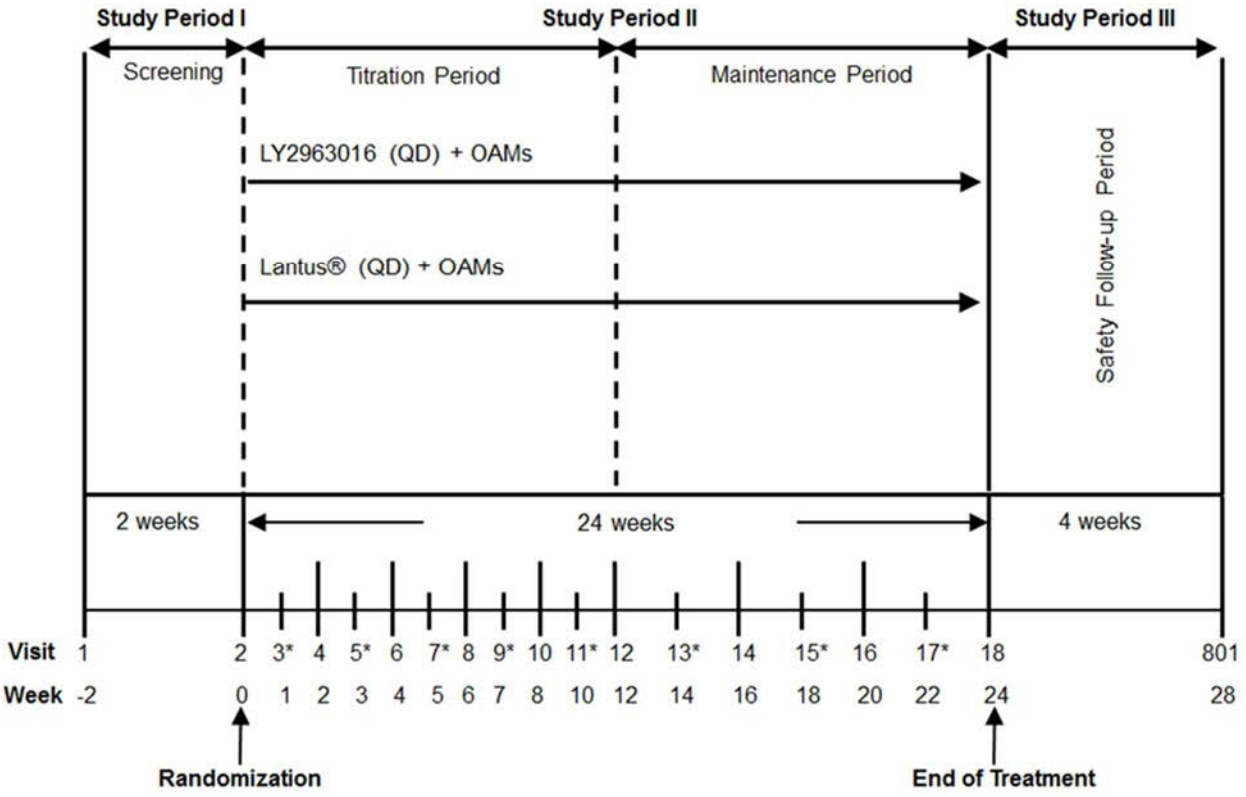
A total of 530 patients are planned to be enrolled in the study, with a target to complete 450 patients. Patients will be screened at Visit 1, and eligible patients will be randomized at Visit 2 to receive LY2963016 or Lantus® QD with at least 2 OAMs for a period of 24 weeks at which the efficacy endpoint of change in HbA1c levels from baseline will be assessed.

Patients will be contacted over the telephone in-between office visits (described as "Telephone Visits" in Section 7.2.2.3.1) to be queried about the entry in their diaries regarding any AEs, hypoglycemia, insulin self-administration, etc.

At approximately 4-week post-treatment endpoint (Visit 801), patients will have a final clinic visit at which information will be collected according to the Study Schedule (Attachment 1). The starting dose is 10 units (U), which will be titrated by the weekly dosing algorithm as described in Section 9.5 until fasting blood glucose (FBG) reaches ≤100 mg/dL (5.6 mmol/L) (weekly-base titration till Visit 10 and titration as needed afterwards. The insulin doses can be adjusted between intervals at discretion of the investigators. The titration procedure during the study will occur as described in Section 9.5.

End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.

Figure ABET.7.1 illustrates the study design.



Abbreviations: OAM = oral antihyperglycemic medication; QD = once daily;
* = telephone visit.

Figure ABET.7.1. Study design for Clinical Protocol I4L-GH-ABET.

7.2. Discussion of Design and Control

7.2.1. Introduction

The present study is a randomized, open-label trial that will compare the efficacy and safety of LY2963016 to Lantus® in patients with T2DM. The study patients will be insulin naïve and on 2 or more OAMs with inadequate glycemic control.

This study is designed to allow comparison of the 2 insulin analogs, with regard to efficacy and safety, when used as a basal insulin therapy in these patient populations. The study design includes the following periods: Screening, Randomization, Treatment Period (composed of a Titration Period and a Maintenance Period), and a Follow-up Period. It is expected that most of the titration will be completed during the Titration Period (Week 0 through Week 12) such that a patient is on a relatively stable basal insulin dose during the Maintenance Period (Weeks 13 through Weeks 24) during which adjustments to insulin dose would be for safety such as hypoglycemia or unacceptable hyperglycemia.

7.2.2. Study Visits

7.2.2.1. Screening (Visit 1)

Approximately 2 weeks prior to the start of the study, all potential study patients eligible for randomization will be screened after signing the informed consent form (ICF) and assigned a patient number. Medical history (including history of previous insulin exposure) and preexisting conditions, physical examination, height, weight, vital signs, electrocardiogram (ECG) readings, concomitant medications, and AEs will be recorded during this visit. Laboratory assessments performed to determine eligibility for the study include pregnancy tests for females of child bearing potential, HbA1c, serum chemistry and hematology assays to be performed at a central laboratory (Attachment 1 and Attachment 2). Patients who do not meet all the inclusion criteria at Visit 1 will be considered screen failures and will not be randomized to participate in the study. Serum pregnancy tests will be performed on all females of childbearing potential at Visit 1 and when clinically indicated. Urine pregnancy tests at other visits can be accepted per local regulations. A urine pregnancy test may be repeated locally for any visits if considered necessary by the investigators and/or in compliance with local regulations.

Each patient will be given a glucometer (and associated supplies) and training on the use of the glucometer to monitor their BG levels (i.e., 4-point and 7-point SMBG) during the study (Section 7.2.3). Qualified medical staff will instruct patients about signs and symptoms of hypoglycemia and hyperglycemia and how to treat them. Patients will be given study diaries and associated training to record all BG levels, insulin doses, episodes of hypoglycemia, AEs, and any medications taken that occur throughout the study (Attachment 1). If allowed by local law, patients may keep the study-provided BG meter at the end of their study participation.

7.2.2.2. Randomization (Visit 2)

7.2.2.2.1. Patients Eligible for Randomization at Visit 2

At Visit 2, additional clinical and laboratory assessments will occur, as outlined in the Study Schedule (Attachment 1). The following activities will occur at this visit:

- Eligible patients will be randomized to 1 of the 2 treatment groups in a ratio of 2:1 (LY2963016 versus Lantus®) by a web directed random assignment that is stratified by HbA1c levels (<8.5% versus ≥8.5%), and entry use of insulin secretagogues (sulfonylurea [SU], meglitinide, neither) .
- Study material (for example, prefilled pen injector) will be dispensed at Visit 2 and at subsequent visits as indicated in the Study Schedule (Attachment 1).
- Patients also will be instructed about diet and exercise and encouraged to maintain their same levels of activity throughout the study.
- Study personnel will train patients on the injection technique of insulin, how to monitor their own BG levels (Section 7.2.3), and proper use of the study diary for recording BG values and corresponding insulin doses, hypoglycemic episodes, and AEs.

- Study diaries from Visit 1 will be collected, and patients will be given a new study diary at Visit 2 and each subsequent investigator-site visit. The diaries will be source documents for the site of the patients' record of their BG levels, insulin doses, and episodes of hypoglycemia that occur throughout the study. The diaries will be collected at each subsequent investigator-site visit to transfer data and used by the investigator to determine any dose adjustments needed for a patient.
- Patient safety will be assessed, including body weight, vital signs, and any AEs or hypoglycemic episodes that occurred since Visit 1. Use of concomitant medications will be noted.
- A blood sample will be drawn to determine the baseline HbA1c level.
- A blood sample will be drawn to determine level of anti-glargine antibodies.
- Blood samples will be drawn and stored during Visit 2 for biomarker assessment as warranted. The sole purpose of this sample storage is to characterize patients' drug response to therapy, for efficacy, lack of efficacy or unforeseen safety signals.
- 7-point SMBG profiles on 2 separate days will be performed in the 2-week period prior to Visit 2 (preferably most recent readings).

7.2.2.2.1.1. Instructions for Insulin Self-Administration

Patients will administer their insulin dose subcutaneously (in the abdomen, upper arm, buttock, or thigh). Patients should be trained by the site personnel on how to inject study insulin and to rotate site injections, following good practices for insulin administration. The initial dose 10 U will be injected by patients under guidance by the investigators at study site (Visit 2). Thereafter, the patient will self-administer insulin dose at bedtime (approximately the same time) starting the day after Visit 2. Dose adjustments for basal insulins are referred to Section 9.5.

Patients will be instructed to monitor themselves for any signs and symptoms of immediate or delayed hypersensitivity or allergic reactions following their injections. Patients will be instructed to contact emergency medical services in case of severe reactions.

7.2.2.3. Study Visits (Visit 3 to Visit 18)

Patients' office visits will occur every 2 weeks between Visit 2 and Visit 10 and every 4 weeks between Visit 10 and Visit 18 (Attachment 1). Additional training may be provided as deemed necessary during Visit 3 to Visit 18 on diary use, insulin injection technique, diet and exercise, or glucometer use.

Between each office visit, there are telephone visits (Visits 3, 5, 7, 9, 11, 13, 15, and Visit 17), which are described separately.

7.2.2.3.1. Telephone Visits (Visits 3, 5, 7, 9, 11, 13, 15, and Visit 17)

Between each office visit, patients will have a telephone visit with the investigator at 1-week intervals after Visits 2, 4, 6, and Visit 8 and at 2-week intervals after Visits 10, 12, 14, and 16.

The main purpose of telephone visits is to check SMBG values. Because the study diaries are considered to be source documents, applicable data from telephone visits will be included and entered in the electronic case report form (eCRF) from the patient diary as part of the next office visit.

During telephone visits, the investigator or designee will inquire, record, and/or perform the following:

- Blood glucose readings from the 4-point SMBG (once before each meal and at bedtime) from 3 separate days (preferably most recent readings) (Attachment 1) since the last office visit (see Section 7.2.3 for further explanation). Note that these values will need to be entered into the eCRF at the next office visit, once the values have been correlated with the study diary values.
- Hypoglycemic episodes since last visit.
- Previous day's insulin dose.
- Adjustment of insulin dose, if applicable.
- Any AEs experienced and any changes in medications since last visit.
- Reeducation of the patient as needed.
- Preparation for next office visit.

Patients will retrieve information about BG values, previous day's insulin dose, and hypoglycemic episodes from entries in their study diaries. Telephone visits can also be conducted as office visits at the study site, if more practical. Although 8 official telephone visits have been planned for this study, investigators may contact patients as frequently as necessary to adjust the insulin dose to achieve BG targets. Specified data from telephone visits (Attachment 1) will be recorded in the eCRFs from the diaries once they are collected from the patient at the next office visit.

7.2.2.3.2. Office Visits (Visits 4, 6, 8, 10, 12, 14, 16, and Visit 18 or Early Discontinuation)

The following activities occur during investigator site Visits 4, 6, 8, 10, 12, 14, 16, and Visit 18 or Early Discontinuation (ED):

- study diaries collected and reviewed for BG levels, episodes of hypoglycemia, insulin self-administration (Section 7.2.2.2)
- distribute study diaries (not completed at ED)
- dispense study drug with prefilled pen injector (not completed at Visits 4, 8, 18, or ED)
- collect study drug at Visits 6, 10, 12, 14, 16, 18, and ED
- collection of blood sample for HbA1c assessment to determine efficacy of treatment values for each patient at Visits 6, 10, 12, 14, 16, 18 or ED

- blood sampling for chemistry and hematology at Visit 18 or ED
- transfer data from study diaries into eCRF (including previous day's insulin dose from last telephone visit)
- adjustment of insulin doses as needed during Visits 4, 6, 8, 10, 12, 14, and Visit 16 (not completed at Visits 18 or ED)
- previous day's insulin dose
- assessment of vital signs, body weight
- inquiries of AEs
- inquire about use of concomitant medications
- collection of blood sample to determine generation of anti-glargine antibodies at Visits 4, 6, 12, and Visit 18 (or ED)
- collection of serum samples for biomarker analysis during Visit 10 and Visit 18
- administer the ITSQ questionnaires during Visits 6, 12, and Visit 18 (or ED)
- dispense BG monitoring supplies as required

In addition to the daily BG monitoring, patients will be instructed to complete:

- 7-point SMBG profiles (described in Section 7.2.3) on 2 separate days in the 2-week period prior to Visits 4, 8, 12, and 18 (or at ED) (preferably most recent readings).
- 4-point SMBG values recorded (once before each meal and at bedtime) on 3 separate days before phone visits then transferred to the eCRF in succeeding office visit (preferably most recent readings).

Patients are instructed on a post-treatment insulin regimen which is at discretion of the investigator (at Visit 18 or ED).

7.2.2.4. Follow-up Visit (Visit 801)

Patients will come to the investigator site approximately 4 weeks after the last treatment visit, at which time information will be discussed and recorded according to the Study Schedule (Attachment 1). Note: The previous day's insulin dose will be recorded if the patient has continued to take insulin.

Patients who discontinue early from the study will undergo all the end of study procedures and complete Visit 801 as outlined in Attachment 1.

7.2.3. Blood Glucose Monitoring Plan

Patients will be provided with glucometers and corresponding glucose test strips so they can obtain SMBG values. Blood glucose values will be utilized to guide insulin titration dosing; to determine hypoglycemia, as specified in the protocol; and to ensure that uniform data are collected. Glucose test strips will be distributed according to national regulations.

Throughout the study, patients will be instructed to check their FBG values daily to assess the need for dose adjustments. The first recorded BG value for each profile should be a premorning meal BG value followed by the other specified BG values through the day for consistency.

- In the week prior to telephone visits, patients will be instructed to complete 4-point SMBG values (once before each meal and at bedtime) recorded on 3 separate days (preferably most recent readings). Four-point SMBG values reported during telephone visits will be recorded at the subsequent office visit and Visit 801.
- Patients will be instructed to complete 7-point SMBG profiles on 2 separate days in the 2-week period prior to Visits 2, 4, 8, 12, and 18 (preferably most recent readings). The SMBG profiles will consist of:
    - before the morning meal, midday meal, and evening meal; 2-hour postprandial measurements for the morning, midday meal, and evening meal; at bedtime.
    - In case of unexplained morning hyperglycemia, investigators shall instruct patients to conduct additional 3am and prebreakfast BG to identify the cause.

Missing values in SMBG profiles that do not reflect noncompliance with the protocol, in the opinion of the investigator, will not be considered a protocol deviation.

Patients may be requested by investigators to perform more intensive self-monitoring, if clinically indicated. Patients should record all BG values in their study diaries.

The morning premeal measurement should be done fasting before breakfast. Data from the 7-point SMBG profiles measured prior to Visits 2, 4, 8, 12, and 18 will be used to assess the effect of the treatments on daily BG values and should, therefore, be transferred to the eCRF at those visits. In the case of ED, 7-point SMBG values from the patient's study diary after the previous office visit should be entered into the eCRF, as are available. Patients should record all BG values (and insulin doses after Visit 2) in their study diaries.

8. Study Population

Patients who give written informed consent will be entered at Visit 1. Patients who meet all of the inclusion/exclusion criteria will be randomized at Visit 2 and will receive study drug.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

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

8.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] Have T2DM based on the disease diagnostic criteria World Health Organization (WHO) classification (see Attachment 5).

[2] If female patients, are women of child-bearing potential who test negative for pregnancy at the time of enrollment based on a serum pregnancy test and agree to use a reliable method of birth control during the study.

[3] Are ≥18 years of age.

[4] Have been receiving 2 or more OAMs at stable doses for the 12 weeks prior to Visit 1. Note: use and dose of oral agents in combination with insulin must be in accordance with the local product label. Doses of any OAMs are required to have been stable for the 12 weeks prior to Visit 1 and at least 2 of the OAMs must be dosed at or above half the maximum daily dose allowed by local regulations.

Patients taking metformin and who are found to have a contraindicated serum creatinine level (≥1.4 mg/dL [124 µmol/L] for females, ≥1.5 mg/dL [133 µmol/L] for males) must be willing to discontinue use of metformin at randomization.

Note: If on 2 OAMs at study entry and there is a need to discontinue one of those agents due to country labeling requirements or clinical parameters, that patient would not meet entry criteria.

[5] Have an HbA1c ≥7.0% and ≤11.0%.

[6] Body mass index (BMI) ≤35 kg/m^2.

[7] As determined by the investigator, are capable and willing to do the following:

- perform SMBG
- complete patient diaries as required
- use prefilled pen injector according to study instructions

- are receptive to diabetes education
- comply with required study treatment and study visits

[8] Have given written informed consent to participate in this study in accordance with local regulations.

8.2. Exclusion Criteria

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

[9] Have used insulin therapy (outside of pregnancy) anytime in the past 1years, except for short-term treatment of acute conditions, and up to a maximum of 4 continuous weeks. Insulin use of any duration during pregnancy is not considered an exclusion criterion.

[10] Have used any glucagon like peptide (GLP-1) receptor agonists within the previous 90 days.

[11] Are currently taking traditional medicine (herbal medicine or patent medicine) with known/specified content of anti-hyperglycemic effects within 3 months before Visit 1.

[12] Have had more than one episode of severe hypoglycemia within 6 months prior to entry into the study.

[13] Have had ≥2 emergency room visits or hospitalizations due to poor glucose control (e.g., ketoacidosis or hyperosmolar coma) in the 6 months prior to Visit 1.

[14] Have known hypersensitivity or allergy to Lantus® or its excipients.

[15] Are receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy at pharmacological doses (excluding topical, intra-articular, intraocular, or inhaled preparations and physiologic replacement doses for adrenal deficiency) or have received such therapy within 4 weeks immediately preceding Visit 1.

[16] Have obvious signs or symptoms, or laboratory evidence, of liver disease (alanine aminotransferase [ALT]; or aspartate aminotransferase [AST] greater than 2.5 times the upper limit of the reference range, as defined by the central laboratory; or albumin value remarkably above or below the normal reference range, as defined by the central laboratory).

[17] Have one of the following concomitant diseases: significant cardiac (for example, congestive heart failure Class III or IV) or gastrointestinal disease (for example, significant gastroparesis).

[18] Have a history of renal transplantation, are currently receiving renal dialysis or have a serum creatinine greater than 2.0 mg/dL (177 μmol/L).

[19] Have had a blood transfusion or severe blood loss within 3 months prior to Visit 1 or have known hemoglobinopathy, hemolytic anemia, or sickle cell anemia.

[20] Patients with active cancer or personal history of cancer within the previous 5 years (with the exception of basal cell carcinoma or carcinoma in situ).

[21] Have a history or diagnosis of human immunodeficiency virus (HIV) infection.

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

[23] Have any other condition (including known drug or alcohol abuse or psychiatric disorder) that precludes the patient from following and completing the protocol.

[24] Are Lilly or Boehringer Ingelheim employees.

[25] Are currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[26] Have previously completed or withdrawn from this study.

[27] Are pregnant or intend to become pregnant during the course of the study, or are sexually active women of childbearing potential not actively practicing birth control by a method determined by the investigator to be medically acceptable.

[28] Are women who are breastfeeding.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criterion [9] excludes patients who have received chronic insulin therapy except short-term treatment.

Exclusion criteria [10 and 19] exclude medications or conditions that may cause HbA1c lowering not attributable to the regimens being studied, or which could lead to misinterpretation of the results.

Exclusion criterion [11] excludes traditional medicine with anti-hyperglycemic effects due to safety concerns and leading to misinterpretation of the results.

Exclusion criterion [12] and [13] addresses the potential difficulty of distinguishing if severe hypoglycemia is related to study drugs or to poor glycemic control in patients with recurring episodes.

Exclusion criteria [14 to 21] represent clinical situations that may prevent patients from completing the protocol, or may influence the effect or safety of study regimens, or are serious

conditions that pose a risk for morbidity and mortality. Exclusion criterion [20] allows investigators to exclude patients in whom there may be a concern for cancer occurrence or recurrence consistent with the ADA-American Cancer Society (ACS) consensus report's recommendation. According to this recommendation, patients with a very high risk of cancer occurrence (or for recurrence of specific cancer types) may require more careful consideration in choosing between available diabetes therapies (Giovannucci et al. 2010).

Exclusion criterion [15] relates to the negative effect of steroid therapy on the management of diabetes.

Exclusion criterion [23] permits investigators to exclude patients who meet all other inclusion and exclusion criteria but may not be appropriate study candidates.

Exclusion criteria [22] and [24] reduce potential bias due to conflict of interest.

Exclusion criterion [25] prevents a situation in which potential positive or negative outcomes may not be clearly attributable to the regimens in the study.

Exclusion criterion [26] eliminates the possibility of duplicate participation by a patient.

Exclusion Criteria [27] and [28] assure the safety of unborn or newborn children.

8.3. Discontinuations

8.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly.

If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the subject to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

8.3.2. Discontinuation of Investigational Product

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

- ALT or AST >8X upper limit of normal (ULN)
- ALT or AST >5X ULN for more than 2 weeks

- ALT or AST >3X ULN and total bilirubin level >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients who discontinue the investigational product and/or study early will have ED procedures performed as shown in the Study Schedule (Attachment 1).

8.3.3. Patient Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- If any of Exclusion criteria ([14 to 15], [17 to 20], [23], [25], and [27 to 28]) are observed or develop after entry. In this case, the patient may be discontinued from the study at the next visit, or sooner, if patient safety is the rationale for the exclusion criterion
- If there is a lack of efficacy or the need to intensify the patient's treatment (Section 9.5.1) beyond basal insulin dosing, based on investigator discretion that the patient has not had adequate progress in the reduction of HbA1c levels in spite of adequate basal insulin titration and dosing. For example: Based on investigator clinical judgment, a patient may be deemed appropriate to discontinue from the study if he/she is consistently achieving target FBG levels ≤100 mg/dL (5.6 mmol/L), but HbA1c levels remain above 8.0% on at least 2 consecutive occasions in the absence of any signs of continued improvement. Or, a patient may be deemed appropriate to discontinue from the study if he/she is not achieving target FBG levels ≤100 mg/dL (5.6 mmol/L) but is experiencing hypoglycemia that would preclude further basal insulin titration
- If the patient is off study medication for more than 14 consecutive days
- If the patient has used short/rapid-acting insulin for glucose control and management of diabetes during an acute illness/injury for more than 14 consecutive days
- If the patient enrolls in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Investigator Decision
    - if the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Subject Decision
    - if the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study
- Sponsor Decision

  - if Lilly or its designee stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP

- Adverse Event
  - if the investigator decides that the patient should be withdrawn because of an SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations Section 10.3.

Randomized patients who discontinue the study early will have early discontinuation procedures performed as shown in the Study Schedule (Attachment 1).

8.3.4. Patients Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8.3.5. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8.3.6. Discontinuation of the Study

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

9. Treatment

9.1. Treatments Administered

All treatments will be administered within the product labeling in China, when applicable. For LY2963016, administration is described in the protocol. This study involves a comparison of LY2963016 to Lantus® administered QD subcutaneously. Patients will continue their prestudy OAMs throughout the study.

Lantus® or LY2963016 will be started from 10 U based on randomization. Investigators will titrate insulins until a FBG ≤100 mg/dL (5.6 mmol/L). The dosing algorithm is referred to Section 9.5. The investigators will be responsible for dose adjustment in telephone or office visits. The insulin doses can be adjusted between the intervals of visits at discretion of the investigators.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the patient,
- 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.

Patients taking insulin secretagogues must continue taking their prescribed dose throughout the study. If the patient experiences hypoglycemia, the investigator should assess whether it can be attributed to causes other than the insulin secretagogue, such as missed meals, other changes in diet or exercise, or incorrect dosing/administration of insulin. The investigator may decrease the dose or discontinue the insulin secretagogue only after consultation and approval by the Lilly CRP or designee, and this must be documented appropriately.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.2. Materials and Supplies

Clinical trial materials will be labeled and should be handled and stored according to the respective country's regulatory requirements.

The reference therapy (Lantus®) used in this clinical trial is approved for use in each respective country.

Patients must continue to use their prestudy OAMs throughout the study (Section 9.8.1). Patients on metformin must continue or discontinue the use of metformin based on Inclusion Criterion [4].

Patients randomized to LY2963016 will be provided with LY2963016 as a 100 U/mL solution for injection in a prefilled pen injector. Patients randomized to Lantus® will be provided with Lantus® as a 100 U/mL solution for injection in prefilled pen injector. In addition, a commercially available glucometer will be provided with the necessary supplies.

9.3. Method of Assignment to Treatment

At Visit 1, patients will be assigned a patient number, and at Visit 2, those who are eligible to participate in the study will be assigned to 1 of the 2 treatment arms in a ratio of 2:1 (LY2963016 versus Lantus®) by stratified randomization via random assignment using the interactive web response system (IWRS). To achieve group comparability, patients will be stratified by HbA1c stratum (<8.5%, ≥8.5%), and entry use of insulin secretagogues (SU, meglitinide, neither).

9.4. Rationale for Selection of Doses in the Study

Patients in both treatment groups will start with a single injection of basal insulin analog (either Lantus® or LY2963016). As supported by nonclinical data demonstrating similar glucodynamics between Lantus® and LY2963016 (data on file), and clinical data demonstrating similar efficacy and safety between Lantus® and LY2963016 (Blevins et al. 2015; Rosenstock et al. 2015), these insulins will be dosed in a similar fashion based on the dosing algorithm described in the protocol.

Patients will be started on 10 U of Lantus® or LY2963016, based on randomization. Investigators will titrate insulins until a FBG ≤100 mg/dL (5.6 mmol/L) is achieved as described in Section 9.5. It is expected that most of the titration will be completed during the Titration Period (Weeks 0 through 12) such that a patient is on a relatively stable basal insulin dose during the Maintenance Period (Weeks 13 through 24) during which adjustments to insulin dose would be for safety such as hypoglycemia or unacceptable hyperglycemia.

Patients will continue to use their prestudy OAMs throughout the study.

9.5. Selection and Timing of Doses

All treatments will be administered according to the country-specific product labeling where applicable. The starting dose for patients is 10 U QD. The study insulin will be self-administered by the patient at bedtime (approximately the same time) from the following day after Visit 2. The dosing time is chosen based on the China guideline for type 2 diabetes on initiation of basal insulin (Chinese Diabetes Society 2014).

Dose titration is investigator-driven. From the telephone visit (Visit 3), the investigator will assess the patient's glycemic control for the previous week (weekly-base titration till Visit 10 and bi-weekly titration as needed afterwards) and, if necessary, inform the patient about any needed dose adjustment. The dose will be adjusted using the following dosing algorithm based on the patient's BG.

Following initiation of LY2963016 or insulin glargine, investigators may make alterations to increase the doses recommended by the dose adjustment algorithm in situations where adjustment have not had the desired therapeutic effect after consultation with Lilly. Dose increases must be made at weekly intervals within 8 weeks from study initiation and as needed in the rest of treatment. The insulin doses can be adjusted between the intervals at discretion of the investigators.

The treat-to-target FBG is ≤100 mg/dL (5.6 mmol/L). The insulin dose titration will be based on the glucose pattern from 3 separate BG readings before breakfast (preferably most recent readings) prior to each contact/visit from previous 1-2 weeks. The dose algorithm for LY2963016 or insulin glargine will be referred to Table ABET.9.1 (Davies et al. 2005).

Table ABET.9.1. Algorithm for Titration of Basal Insulin Dose

Average BG Before Breakfast (for Titration of Evening Dose)	Increase in Basal Dose (Units)
<70 mg/dL (<3.9 mmol/L)	Decrease to previous lower dose*
70-<100 mg/dL (3.9-5.6 mmol/L)	No adjustment
100-<120 mg/dL (5.6-6.7 mmol/L)	0-+2 U (at discretion of the investigator)
120-<140 mg/dL (6.7-7.8 mmol/L)	+ 2 U
140-<180 mg/dL (7.8-10.0 mmol/L)	+ 4 U
≥180 mg/dL (>10.0 mmol/L)	+6-8 U (at discretion of the investigator)

* The patient will be administered with the previous lower dose if he/she has documented hypoglycemia or probable symptomatic hypoglycemia.

Abbreviations: BG = blood glucose; U = unit(s).

The investigators will also have the discretion to decrease the dose if it is noted that patients are experiencing hypoglycemia. Patients will continue to take prestudy OAMs at the same dose during the study, unless described otherwise for certain conditions prespecified in the protocol (Section 9.8). The investigator may decrease the dose or discontinue the insulin secretagogue only after consultation and approval by the Lilly CRP or designee, and this must be documented on a note-to-file.

9.5.1. Special Treatment Considerations

There is no plan for rescue therapy in this study. Patients who do not respond to basal insulin treatment for glycemic control will be discontinued from the study as described in Section 8.3.1.

9.6. Continued Access to Investigational Product

The Sponsor will not provide patients with ongoing supplies of study medication after they have completed the study treatment period because LY2963016 is experimental.

9.7. Blinding

This is an open-label study where investigators, patients, study-site personnel, and study monitors are aware of the treatment assignment. To minimize bias, an integrated summary of data will not be provided by the actual treatment group to the study team prior to the final database lock. Unblinding of the patient study drug treatment assignment to the study team may occur in cases when an individual patient's treatment assignment may need to be revealed for evaluation of the safety information or during review of SAEs or individual patient data.

9.8. Concomitant Therapy

9.8.1. Antihyperglycemic Medications

Generally, patients should continue use of their OAM regimen at screening and as described in Inclusion Criterion [4] (Section 8.1). The investigator will carefully consider the potential drug-drug interactions and contraindications of the OAMs with respect to the study insulins. Patients will not be allowed any other medications to reduce BG besides those outlined in Exclusion Criterion [11] (Section 8.2).

Patients taking insulin scretagogues must continue taking their prescribed dose throughout the study. If the patient experiences hypoglycemia, the investigator should assess whether it can be attributed to causes other than the insulin scretagogues, such as missed meals, other changes in diet or exercise, or incorrect dosing/administration of insulin. The investigator may decrease the dose or discontinue the insulin scretagogues only after consultation and approval by the Lilly CRP or designee, and this must be documented appropriately.

The intent of this study is that patients not deviate from their OAM regimen and that they only use the study insulin(s) prescribed for them during the study. However, in emergencies, it may be necessary for patients to change their dose of OAMs and/or be treated with a nonstudy insulin. This will be allowed for up to 14 consecutive days. If such a situation occurs more than once during the study, or lasts longer than 14 consecutive days, a decision to keep the patient in the study should be made only after consultation between the investigator and the Lilly CRP or medical designee. The decision should be documented by a note to the investigator's file.

Please refer to Section 8.3.1 to review the criteria for discontinuation of patients.

9.8.2. Other Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study.

As described in Exclusion Criteria [9 to 11] (Section 8.2), patients should not take any other BG-lowering medications of any kind that are not allowed in the study. Patients will be allowed to use any other concomitant medications they require during the study except systemic glucocorticoid therapy longer than 14 consecutive days' duration (with the exception of topical, intra-articular, intraocular, and inhaled preparations). Patients who receive excluded concomitant therapy will be discontinued from the study (Section 8.3.1).

9.9. Treatment Compliance

The investigator will assess patient compliance at each visit, based on a review of the patient's glycemic control, adherence to the visit schedule, dosing-titration algorithm, administration of study drug (including dosing time), completion of study diaries, and any other parameters the investigator deems necessary.

Patients who are deemed noncompliant will receive additional diabetes education and training, as required, and the importance of compliance with the protocol will be reinforced. Patients who,

in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from the study. No specific study data will be collected for analysis of treatment compliance and, therefore, will not be assessed or reported.

9.10. Hypoglycemic Episodes

Patients should check their BG level, whenever possible, if they have symptoms suggestive of hypoglycemia. For each hypoglycemic episode, patients should record their BG level, associated symptoms, treatment, and outcome in the study diaries provided by the Sponsor via the investigator.

When instructing patients on recognition and management of hypoglycemic episodes, a **hypoglycemic episode** is defined as any time a patient feels that he/she is experiencing a sign or symptom that is associated with hypoglycemia, or has a BG level of ≤70 mg/dL (≤3.9 mmol/L), even if it was not associated with signs, symptoms, or treatment consistent with current guidelines (ADA 2005).

Note: Episodes of severe hypoglycemia reported during the study should also be recorded as SAEs (Section 10.3.1.1).

Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status, and cannot assist in his/her care, are semiconscious or unconscious, or experience coma with or without seizures, and may require parenteral therapy. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG ≤70 mg/dL [3.9 mmol/L]).

Nocturnal hypoglycemia: Any hypoglycemic event that occurs between bedtime and waking.

Documented Hypoglycemia:

- **Documented symptomatic hypoglycemia:** An event during which typical symptoms of hypoglycemia are accompanied by plasma glucose (PG) ≤70 mg/dL (≤3.9 mmol/L).
- **Documented asymptomatic hypoglycemia:** An event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (≤3.9 mmol/L).
- **Documented unspecified hypoglycemia**: An event during which PG ≤70 mg/dL (≤3.9 mmol/L) but no information relative to symptoms of hypoglycemia was recorded.

Probable symptomatic hypoglycemia: An event during which symptoms typical of hypoglycemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤70 mg/dL (≤3.9 mmol/L).

Relative hypoglycemia (also referred to as Pseudohypoglycemia): An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured PG concentration >70 mg/dL (>3.9 mmol/L) but approaching that level.

Overall hypoglycemia: This optional category combines all cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia) excluding the events of relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in this category.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Measure

The primary efficacy measure is the change in HbA1c from baseline to 24 weeks.

10.1.2. Secondary Efficacy Measures

The following measures will be considered for the comparison of other aspects of overall glycemic control:

- change in HbA1c from baseline to 4, 8, 12, 16, and 20 weeks or LOCF
- percentage of patients with HbA1c <7%; percentage of patients with HbA1c ≤6.5%
- 7-point SMBG measurements, as listed in the Study Schedule (Attachment 1)
    - premeal for each meal
    - postmeal for each meal
    - bedtime
- intrapatient variability, as measured by the standard deviation of the 7-point SMBG.Basal insulin dose (including U/day and U/kg/d)
- weight change
- patient-reported outcomes as reflected in responses to ITSQ

10.2. Health Outcome/Quality of Life Measures

Self-reported patient questionnaires will be utilized to compare health outcomes for the 2 insulins being studied. These health outcomes, specific to treatment satisfaction, will be reflected in responses to ITSQ administered at Visits 6, 12, Visit 18 and ED if a patient received at least one dose of study insulin.

The ITSQ is a validated instrument containing 22 items that assesses treatment satisfaction for persons with diabetes on insulin (Anderson et al. 2004). Items are measured on a 7-point scale, where lower scores reflect better outcomes. In addition to an overall score, the items that make up the 5 domains of satisfaction are categorized as:

- Inconvenience of Regimen (IR - 5 items)
- Lifestyle Flexibility (LF - 3 items)

- Glycemic Control (GC - 3 items)
- Hypoglycemic Control (HC - 5 items)
- Satisfaction with the Insulin Delivery Device (DD - 6 items)

All individual patient-domain scores will be calculated as the sum of the items in the domain. If item score is missing and less than 20% of the items within the domain are missing for that patient, then the mean of all other patients' scores for that item will be imputed for the item. Otherwise, the domain score will be missing for the patient.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious (SAEs), considered related to the study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.3.1. Adverse Events

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

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease while under treatment in the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

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

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

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

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the investigational product, the following terminologies are defined:

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Unrelated**: without question, the AE is definitely not associated with the study treatment

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study-site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

Serious adverse event collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

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

Study site personnel must alert Lilly or its designee via a sponsor-approved method of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts 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.

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

- 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
- that which is considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For the purposes of this protocol, all episodes of severe hypoglycemia will be considered an SAE. If the investigator believes that a reported SAE of hypoglycemia does not meet any of the specific criteria outlined above (that is, death, initial or prolonged inpatient hospitalization, a life-threatening experience, persistent or significant disability/ incapacity, or congenital anomaly/birth defect), the outcome of "considered significant by the investigator for any other reason" should be selected in the eCRF.

When a condition related to LY2963016 or Lantus® 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.

Serious adverse events occurring up to and including the patient's last visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

Pregnancy (during 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.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient 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.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. Lilly has procedures for the recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and detailed guidances and will be followed.

10.3.2. Other Safety Measures

Hypoglycemic events, vital signs, and weight will be collected as indicated in the Study Schedule (Attachment 1). Twelve-lead ECGs will be collected locally according to the Study Schedule (Attachment 1).

The ECG 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 patient is still present, for immediate patient management and to determine whether the patient meets entry criteria.

10.3.3. Safety Monitoring

The Lilly CRP or medical designee will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP or medical designee will, as is appropriate, consult with the functionally independent GPS therapeutic area physician or clinical scientist, and periodically review:

- trends in safety data
- laboratory analytes
- adverse events

If a study patient experiences elevated ALT or AST ≥ 3X ULN or elevated total bilirubin ≥ 2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 2 and Attachment 4.

10.3.4. Complaint Handling

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

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 and any associated AEs using study-specific product-complaint forms, which are provided for this purpose
- faxing the completed study-specific 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 study-specific product-complaint form along with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific laboratory tests that will be performed for this study.

Attachment 3 provides a summary of the estimated maximum number and volume of samples, for all sampling, during the study.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry and hematology will be performed. The clinical laboratory tests including a pregnancy test will be performed at a central laboratory. A urine pregnancy test may be repeated locally for any visits if considered necessary by the investigators and/or in compliance with local regulations. Attachment 2 lists the specific tests that will be performed for this study.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of the 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.

10.4.2. Samples for Biomarker Research

10.4.2.1. Nonpharmacogenetic Biomarker Evaluations

This study will employ sample collection. Samples will be collected for nonpharmacogenetic biomarker investigation where local regulations allow. Fasting serum samples will be collected at the times specified in the Study Schedule (Attachment 1).

Fasting samples being collected will be used to measure C-peptide to support trial interpretation.

Samples will be coded with the patient number and may be stored for a maximum of 1 year following last patient visit for the trial at a facility selected by the Sponsor to enable further analysis of responses to the investigational products. The duration allows the Sponsor to respond to regulatory requests related to the investigational products.

10.4.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against LY2963016 or Lantus®. Immunogenicity will be assessed by a validated assay designed to detect anti-glargine antibodies in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the LY2963016 or Lantus®.

Samples may be stored for a maximum of 1 year following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to LY2963016 or Lantus®. The duration allows the sponsor to respond to regulatory requests related to the investigational product.

10.5. Appropriateness of Measurements

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to diabetes mellitus.

11. 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 use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the Sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

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.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect PRO measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Based on the primary objective, to show noninferiority of LY2963016 to Lantus® at the 0.40% noninferiority margin (NIM), 450 completers in total with a ratio 2:1 (LY2963016 versus Lantus®) are needed at 24 weeks. This calculation assumes no treatment difference in HbA1c between LY2963016 and Lantus®, common SD of 1.3% for change from baseline in HbA1c, 0.05 two-sided significance level, and over 85% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients is 530 in total (353 for LY2963016 and 177 for Lantus®).

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

All data will be entered, verified, and archived by a contract research organization (CRO) external to Lilly and/or at Lilly. Data listings, summaries, and analyses will be performed by a CRO and/or by Lilly under the guidance and approval of statisticians at Lilly. Statistical analysis of this study will be the responsibility of Lilly.

Any change to the data-analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan and/or in the clinical study report (CSR). Additional exploratory analyses will be conducted as deemed appropriate.

The patient populations used in the study are described below:

1. All Patients Entered - all patients who entered this study and completed Visit 1
2. All Randomized - all patients who were randomized to a treatment arm
3. Full Analysis Set (FAS) - based on the intent to treat (ITT) principle, all patients who were randomized and who have taken at least one dose of study medication will be included in this analysis set. Patients will be analyzed according to the treatments to which they were randomized.
4. Per-protocol (PP) - patients in the FAS/ITT population who also meet the following criteria:
    a. have no violations of Inclusion/Exclusion Criteria
    b. have not discontinued from the study prior to 24 weeks
    c. have not been off study medication for more than 14 consecutive days during the treatment period
    d. have not received chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, intraocular, and inhaled preparations)

Efficacy and safety analyses will be conducted using the FAS population. Selected analyses will be conducted using the All Randomized population and the PP population.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated as 2-sided 95% CIs. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.05. No adjustments for multiplicity will be performed.

The baseline is Visit 2. If baseline data are missing, the last measurement taken prior to this visit will be used for the baseline measurement.

The analysis of the continuous secondary efficacy and safety measurements will use the same mixed model repeated measure (MMRM) model for the primary efficacy analyses with the baseline value of the response as a covariate with the FAS patient population. Continuous laboratory measures will be analyzed using an analysis of covariance (ANCOVA) model. For categorical measures, Fisher's exact test or Pearson's Chi-square test will be used.

All analyses will be implemented using SAS Version 8.2® or higher.

12.2.2. Patient Disposition

All patients 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.

A listing of the primary reason for patient discontinuation will be presented for all randomized patients. Summary analyses will be conducted for the randomized and FAS populations. Frequency counts and percentages will be presented for each treatment group and compared across treatment groups using Fisher's exact test or Pearson's Chi-square test.

12.2.3. Patient Characteristics

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

Demographic and baseline characteristics will be summarized by treatment group for the FAS and PP populations. For continuous measures, summary statistics will include sample size, mean, median, maximum, minimum and SDs. The treatment groups will be compared using a 2-sample *t* test. For categorical measures, summary statistics will include sample size, frequency, and percent. Analysis will use Fisher's exact test or Pearson's Chi-square test.

12.2.4. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by different categories and treatment group using the FAS population. All concomitant therapies that originally mapped using the WHODRUG dictionary in the Clintrial database will be further classified using anatomical therapeutic chemical codes for reporting purposes. Analysis will use Fisher's exact test or Pearson's Chi-square test.

12.2.5. Treatment Compliance

No specific study data will be collected for analysis of treatment compliance.

12.2.6. Primary Efficacy Outcome and Methodology

The primary efficacy outcome will be the change in HbA1c level from baseline to 24 weeks. The primary analysis will be a likelihood-based, MMRM approach, treating the data as missing at random (MAR) for the FAS population. The MMRM model will evaluate the change from baseline to each post-baseline visit in HbA1c level as the dependent variable with treatment (LY2963016, Lantus®), entry use of insulin scretagogue (SU, meglitinide, neither), visit, and interaction between visit and treatment as fixed effects; the baseline value of HbA1c as a covariate; and a random effect for patient. The MMRM model will be carried out using the observed margins (OM) option in SAS. Using this option weights the levels of the independent or stratification variables according to the observed marginal distribution. This will provide least-squares means (LSMeans) for these outcomes that are more representative of the patient population recruited in this study.

The primary treatment comparison is to compare LY2963016 versus Lantus® at the NIM of +0.4%. If the upper limit of the 95% CI on the change from baseline to 24-week endpoint HbA1c for LY2963016 versus Lantus® is below +0.4%, then LY2963016 will be declared noninferior to Lantus®. The LSMean and standard error derived from the MMRM model for each treatment will be used to test noninferiority. Type III sums of squares will be used to make the treatment comparisons.

- If the +0.4% NIM is met, a key secondary treatment comparison is to compare Lantus® versus LY2963016 at the NIM of -0.4%. If the lower limit of the 95% CI on the change in HbA1c from baseline to the 24-week endpoint for LY2963016 versus Lantus® is above -0.4%, then Lantus® will be declared noninferior to LY2963016. The LSMean and standard error derived from the MMRM model for each treatment will be used to test noninferiority. This gate-keeping procedure controls the family-wise Type 1 error rate at a 1-sided 0.025 level.
- If LY2963016 is declared noninferior to Lantus® in the primary treatment comparison, and Lantus® is declared noninferior to LY2963016 in this secondary treatment comparison, then LY2963016 will be considered to have equivalent efficacy as Lantus®.

A first secondary analysis of the primary efficacy outcome will use the same MMRM model described above with the PP patient population. Significance tests will be based on LSMeans using the Type III sum of squares, and testing for noninferiority will occur as described above.

A second secondary analysis of the primary efficacy outcome will use an ANCOVA model with FAS population. The ANCOVA model will include treatment and entry use of insulin screatagogue (SU, meglitinide, neither) as fixed effects and the baseline value of HbA1c as a covariate. The ANCOVA model will be carried out using the OM option in SAS. If the 24-week HbA1c value is missing, the last post-baseline value will be carried forward and used in the analysis. This creates the 24-week endpoint value for HbA1c using the LOCF methodology. If

there are no HbA1c data after the date of randomization, the endpoint will be considered missing and the patient will not be included in the analysis.

The analyses of the primary efficacy outcome will only be conducted for patients with both nonmissing baseline value and at least 1 nonmissing post-baseline value.

12.2.7. Secondary Efficacy Outcome and Methodology

The continuous secondary efficacy outcomes include:

- change in HbA1c from baseline to 4, 8, 12, 16, and 20 weeks or LOCF
- 7-point SMBG measurements as listed in the Study Schedule (Attachment 1)
    - premeal for each meal
    - postmeal for each meal
    - bedtime
- intrapatient variability, as measured by the SD of the 7-point SMBG
- basal insulin dose (24-hour total measured in U/d and U/kg) at end of study
- weight change

The analysis of the continuous secondary efficacy variables will be performed using the same MMRM model for the primary efficacy analysis with the baseline value of the response variable added as a covariate with the FAS population. The proportion of patients achieving HbA1c target values (HbA1c level <7.0% and ≤6.5%) at any point during the study (Weeks 4, 8, 12, 16, 20, and 24 and 24-week endpoint [LOCF]) will be analyzed using Fisher's exact test or Pearson's chi-square test.

12.2.8. Health Outcome/Quality of Life Analyses

The ITSQ will be completed at Weeks 4 (Visit 6), 12 (Visit 12) and 24 (Visit 18) or ED. Responses at each of these weeks will be analyzed using the MMRM model for the FAS population as detailed above.

All individual patient-domain scores will be calculated using the nonmissing items and imputing the missing values as the mean of all other patients for the nonmissing items where at least 20% of the items are nonmissing. Otherwise, the domain scores will be missing for the patient.

12.2.9. Safety Analyses

12.2.9.1. Immunogenicity Test Antibodies

The proportion of patients with detected anti-glargine antibodies will be summarized as counts and percentages at baseline, at visit 6 and 12, at the 24-week endpoint (LOCF), and overall for the 24-week treatment period. At each of these time points, the proportion of patients with detected antibodies will be compared between treatment groups using Fisher's exact test. The level of anti-glargine antibodies (percentage binding) will be summarized by descriptive

statistics (mean, median, SD, standard error, minimum, and maximum) at baseline, indicated visits, and endpoint (LOCF). At each of these time points, the level of percentage binding will be compared between treatment groups using the Wilcoxon rank sum test. The relationship between the level of anti-glargine antibodies detected and clinical outcomes (HbA1c, total hypoglycemia, basal dose [U/day, U/kg/day]) will be investigated.

12.2.9.2. Exposure

Duration of exposure to each treatment will be calculated for each patient and summarized by descriptive statistics.

12.2.9.3. Adverse Events

Adverse events will be listed by patient, system organ class, Medical Dictionary for Regulatory Activities® (MedDRA) preferred term, severity, and relationship to the study disease, drug, device, or procedure for all patients. Adverse events (including injection site reactions, allergic events, and neoplasms) will be summarized as TEAEs for the FAS. Treatment-emergent adverse events are defined as events that are newly reported after first study treatment following randomization or reported to have worsened in severity from baseline. The proportion of patients experiencing each TEAE will be presented by preferred term, system organ class, and treatment group. The proportion of patients experiencing each TEAE that is assessed as possibly related to the study disease, drug, device, or procedures will also be summarized. The number of patients and proportion will be presented and compared by treatment using Fisher's exact test or Pearson's chi-square test and will be utilized for the FAS.

Injection site AEs will be evaluated for pain, pruritus, and rash associated with the injection, as well as the characteristics of the injection site (abscess, nodule, lipoatrophy, lipohypertrophy, or induration). The incidences of injection site AEs and allergic events by treatment group will be compared using Fisher's exact test or Pearson's chi-square test for the FAS population.

All SAEs will be listed by patient. If a sufficient number of SAEs are reported, they will be summarized by treatment for all randomized patients. Discontinuations due to TEAEs will be listed by patient. If a sufficient number of discontinuations are reported, they will be summarized by treatment.

12.2.9.4. Hypoglycemic Events

The incidence, rate per 30 days and rate per year of hypoglycemic episodes (total, severe, and nocturnal as defined in Section 9.10) will be summarized by treatment at baseline, titration, maintenance, and overall study periods and at endpoint. The rate per 30 days between two visits is defined as the total number of episodes between the visits divided by the actual number of days between the visits, and then multiplied by 30 days.

The proportion of patients (with at least 1 hypoglycemic event (total, severe, nocturnal, and others) or incidence during the study will be summarized (counts and percentages) and analyzed using Fisher's exact test or the Pearson's chi-square test for the FAS population.

The rate of hypoglycemic episodes per 30 days and per year (total, severe, nocturnal, and others) will be analyzed at baseline, titration, maintenance, and overall study periods and at endpoint

using the Wilcoxon test. In addition, the hypoglycemia rates will also be analyzed using a negative binomial model for the FAS population with terms for treatment, baseline HbA1c, and entry use of insulin secretagogues (SU, meglitinide, neither). The offset variables are log of patient's treatment duration/30 and log of patient's treatment duration/365.25 for the models analyzing hypoglycemia rate per 30 days and per year, respectively.

In addition, the total number of patients with at least 1 hypoglycemic episode divided by the total extent of exposure in patient-years will be calculated for the overall study period and summarized descriptively for each treatment group for total, severe, nocturnal, documented symptomatic, and asymptomatic hypoglycemia definitions only. Listings of hypoglycemic episodes will be presented by visit for each subject.

12.2.9.5. Laboratory Measures

Continuous measures in the chemistry and hematology panels for the FAS population will be summarized at baseline.

Chemistry and hematology laboratory measures will be summarized as change from baseline to each postbaseline visit. The continuous measures and change from baseline values to 24 weeks will be analyzed using the ANCOVA model with treatment, entry use of insulin secretagogues (SU, meglitinide, neither) as fixed effects and the baseline value of HbA1c and the baseline of the response variable as covariates. The ANCOVA model will be carried out using the OM option in SAS.

12.2.9.6. Vital Signs

Systolic blood pressure, diastolic blood pressure, and heart rate will be summarized by descriptive statistics (mean, median, SD, standard error, minimum, and maximum) by visit for the FAS population. Additionally, change from baseline to each postbaseline visit will be summarized. Change from baseline values to each postbaseline visit will be analyzed for the FAS population using the same MMRM model as in the primary efficacy analyses.

12.2.10. Subgroup Analyses

The consistency of the treatment effect will be assessed in the following subgroups in the FAS, if there are a sufficient number of patients in each treatment by subgroup:

- entry HbA1c levels (<7%, ≥7%)
- entry HbA1c levels (<8.5%, ≥8.5%)
- entry BMI (<30, ≥30)
- entry age (<65, ≥65)
- entry use of insulin secretagogues (SU, meglitinide, neither)

The change in HbA1c from baseline to 24-week endpoint will be analyzed using MMRM with treatment, visit, entry use of insulin secretagogues (SU, meglitinide, neither), subgroup, subgroup-by-treatment interaction, subgroup-by-visit interaction, treatment-by-visit interaction,

and treatment-by-visit-by-subgroup interaction as fixed-effects, the baseline value of HbA1c as a covariate, and a random effect for patient for the FAS. If the subgroup is one of the stratification variables, then the subgroup will only be included once in the model. A significant treatment-by-subgroup interaction ($p<.05$) may be indicative of a differential treatment effect across levels of the subgroup, necessitating further exploration of the nature of the interaction.

Other subgroup analyses may be performed if deemed appropriate as exploratory analyses.

12.2.11. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether 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 patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. 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 investigational product
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

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

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

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. 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 investigational product.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

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

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

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). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s).

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

- the current IB or package insert and updates during the course of the study
- ICF
- 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 (CIOMS) International Ethical Guidelines

2) applicable ICH GCP Guidelines

3) applicable laws and regulations

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

Lilly certifies that this study is being conducted under an active United States (US) investigational new drug (IND) application at clinical sites. All investigators (at IND and non-IND sites) are expected to comply with GCP and all applicable local clinical trial regulations.

All or some of the obligations of the Sponsor will be assigned to a third-party organization.

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

13.3.1. Investigator Information

Physicians with a specialty in family practice, internal medicine, or endocrinology, who are experienced in treating patients with diabetes mellitus with basal insulin, may participate as investigators in this clinical trial provided they can demonstrate adequate experience in the conduct of clinical research studies.

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 will sign the final CSR for this study, indicating agreement with the analyses, results, and conclusions of the report.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR 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 ABET Study Schedule

Study Schedule, Protocol I4L-GH-ABET

	Visit																			
Description of Event	**1**	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10**	**11***	**12**	**13***	**14**	**15***	**16**	**17***	**18**	**801**	**ED[#]**
Week of Study	-2	0	1	2	3	4	5	6	7	8	10	12	14	16	18	20	22	24	28	
Allowable Deviation (days)[a]	±7		±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±7	
Telephone Visit			x		x		x		x		x		x		x		x			
Clinic Visit	x	x		x		x		x		x		x		x		x		x	x	x
Screen Inclusion																				
Informed Consent Obtained	x																			
Patient Number Assigned	x																			
Randomization		x																		
Clinic Assessments																				
Medical History and Pre-existing Conditions	x																			
Physical Exam	x																			
Height	x																			
Weight	x	x		x		x		x		x		x		x		x		x		x
Vital Signs (sitting) SBP, DBP, and HR	x	x		x		x		x		x		x		x		x		x		x
Concom Meds[c]	x	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x	x
Adverse Events[c]	x	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x	x
Hypoglycemic Episodes[c]		x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x	x
7-pt SMBG[c,f]		x[e]		x[e]				x[e]				x[e]						x[e]		x[f]
4-pt SMBG[c]			x[c]		x[c]		x[c]		x[c]		x[c]		x[c]		x[c]		x[c]		x	
Previous insulin exposure	x																			
Study Drug/Device																				
Dispense Glucose Meter and Supplies[g]	x	x[g]		x[g]		x[g]		x[g]		x[g]		x[g]		x[g]		x[g]		x[g]		

	Visit																			
Description of Event	**1**	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10**	**11***	**12**	**13***	**14**	**15***	**16**	**17***	**18**	**801**	**ED[#]**
Week of Study	-2	0	1	2	3	4	5	6	7	8	10	12	14	16	18	20	22	24	28	
Allowable Deviation (days)[a]	±7		±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±7	
Telephone Visit			**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**			
Clinic Visit	**x**	**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**	**x**	**x**
Glucometer Training[b]	**x**[b]																			
Dispense Pre-filled Pens		**x**				**x**				**x**		**x**		**x**		**x**				
Training on signs/symptoms of hypo/hyperglycemia[b]	**x**[b]																			
Injection Technique Training[b]		**x**[b]																		
BG Level Monitoring Training[b]	**x**[b]	**x**[b]																		
Distribute Study Diary	**x**	**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**
Diary Use Training[b]	**x**[b]	**x**[b]																		
Diet and Exercise Counseling[b]		**x**[b]																		
Training on Signs/Symptoms of Insulin Reactions		**x**																		
Adjust Insulin Dose (if Applicable)			**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**			
Collect Study Drug						**x**				**x**		**x**		**x**		**x**		**x**		**x**
Collect Study Diary[h]		**x**[h]		**x**[h]		**x**[h]		**x**[h]		**x**[h]		**x**[h]		**x**[h]		**x**[h]		**x**[h]		**x**[h]
Transfer Diary Data to eCRF (InForm™)																				
Insulin Therapy Dose (day prior to visit)			**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
7-pt SMBG Profile[e,f]		**x**[e]		**x**[e]				**x**[e]				**x**[e]						**x**[e]		**x**[f]

	Visit																			
Description of Event	**1**	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10**	**11***	**12**	**13***	**14**	**15***	**16**	**17***	**18**	**801**	**ED[#]**
Week of Study	-2	0	1	2	3	4	5	6	7	8	10	12	14	16	18	20	22	24	28	
Allowable Deviation (days)[a]	±7		±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±7	
Telephone Visit			**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**			
Clinic Visit	**x**	**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**	**x**	**x**
4-pt SMBG[i]				**x**[i]		**x**[i]		**x**[i]		**x**[i]		**x**[i]		**x**[i]		**x**[i]		**x**[i]		**x**[i]
Lab Assessments[j]																				
Chemistry	**x**																	**x**		**x**
Hematology	**x**																	**x**		**x**
Pregnancy Screen[k]	**x**[k]																			
ECG (local)	**x**																			
HbA1c	**x**	**x**				**x**				**x**		**x**		**x**		**x**		**x**		**x**
Anti-Glargine Antibody Titer[l]		**x**[l]		**x**[l]		**x**[l]						**x**[l]						**x**[l]		**x**[l]
Collection of Serum Samples for Biomarkers (Fasting)[d]		**x**[d]								**x**[d]								**x**[d]		**x**[d]
Fasting Serum Glucose[d]		**x**[d]																**x**[d]		**x**[d]
Other - Transfer Data to eCRF (InForm)																				
Administer ITSQ[m,n]						**x**[m]						**x**[m]						**x**[m]		**X**[m,n]

Abbreviations: BG = blood glucose; Concom Meds = concomitant medications; DBP = diastolic blood pressure; eCRF = electronic case report form; ED = early discontinuation; ECG = electrocardiogram; HbA1c = hemoglobin A1c; HR = heart rate; ITSQ = Insulin Treatment Satisfaction Questionnaire; pt = point; SBP = systolic blood pressure; SMBG = self-monitored blood glucose.

* Telephone visit.

\# Patients who discontinue early from the study will complete Visit 801.

a For visit window purposes, the visit will end on the last day the patient completes a study procedure or assessment. Visits should occur within the visit intervals indicated. The timing of visits (including allowable deviations) should be based on time postrandomisation.

b Additional training should be provided as needed throughout the study.

c Adverse events, hypoglycemic episodes, concomitant medications and the last 3 available profiles of 4-point SMBG reported at telephone visits should be recorded on the eCRF at the next office visit. The 4 points are: before morning, mid-day, and evening meals, and at bedtime.

d The measurements should be done fasting before breakfast.

e Patients should perform two 7-point SMBG profiles during the 2-week period prior to these visits (preferably most recent readings). The 7-points are before the morning, midday, and evening meals; 2 hours after the morning, midday meal, and evening meal; at bedtime.

f Transfer values from the study diary if available.

g Dispense glucose meter supplies as needed; may not be at every visit.

h Study sites will retain study diaries.

i The 3 days of 4-point SMBG values used as a reference from the telephone visit need to be validated and entered into the eCRF from the source diaries. These values should be within 1 week (or 2 weeks, if applicable) prior to the telephone visit preceding the office visit when data are transferred to eCRF. In certain instances (for example, between Visits 2 and 4), it may be from the same days as those used for the 7-point SMBGs.

j Analyses should be performed at a central laboratory unless otherwise noted and can be repeated for cause in case of adverse events.

k Serum pregnancy test will be performed on all females of childbearing potential at Visit 1 and when clinically indicated, and will be analyzed by a central laboratory. Urine pregnancy tests at other visits can be accepted per local regulations. A urine pregnancy test may be repeated locally for any visits if considered necessary by the investigators and/or in compliance with local regulations.

l Blood samples for immunogenicity testing will be collected to determine antibody production against LY2963016 or Lantus®.

m Study sites will retain questionnaires.

n This questionnaire should be administered only if the patient has received at least 1 dose of study drug.

Attachment 2. Protocol ABET Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Platelets	Direct bilirubin
Neutrophils, Segmented	Indirect bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Blood urea nitrogen (BUN)
	Creatinine
Other	Albumin
Pregnancy test[b]	
Hemoglobin A_{1c}[a]	**Fasting serum glucose**
Anti-Glargine Antibodies[a]	
Serum for Biomarkers Nonpharmacogenetic	
Biomarkers (C-peptide)	

Abbreviations: RBC = red blood cell; WBC = white blood cell

[a] All laboratory tests to be performed at a central laboratory, unless specified otherwise.

[b] Serum pregnancy tests will be performed on all females of childbearing potential at Visit 1 (and when clinically indicated) and will be analyzed by the central laboratory. Urine pregnancy tests at other visits can be accepted per local regulations. A urine pregnancy test may be repeated locally for any visits if considered necessary by the investigators and/or in compliance with local regulations.

Attachment 3. Protocol ABET Estimated Sampling Summary

This table summarizes the purpose for sampling, sample types, estimated volume per sample, number of samples, and estimated total volume during the study.

Protocol I4L-GH-ABET Sampling Summary

Purpose	Sample Type	Estimated Amount per Sample	Number Samples	Estimated Total Amount
Screening tests[a]	Blood	3 mL	2	6 mL
Standard laboratory tests[a]	Blood	3 mL	9	27 mL
Immunogenicity samples	Blood	8 mL	5	40 mL
Nonpharmacogenetic biomarkers (C-peptide)	Blood	6 mL	3	18 mL
Total				91 mL
Hepatic Monitoring[b]	Blood	-	-	3 - 30 mL

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

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly Designated Medical Monitor.

Attachment 4. Protocol ABET Hepatic Monitoring Tests for Treatment Emergent Abnormality

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transpeptidase; IgG = Immunoglobulin G; IgM = Immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated central laboratory

[b] Reflex/confirmation dependent on regulatory requirement and /or testing availability.

Attachment 5. Protocol ABET World Health Organisation (WHO) Classification of Diabetes

Type 1 Diabetes Mellitus: Type 1 diabetes mellitus is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary, not only to control hyperglycaemia, but to prevent spontaneous ketosis and death.

Type 2 Diabetes Mellitus: Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycaemic symptoms (thirst, polyuria, weight loss), but despite hyperglycaemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in type 2 diabetes, but may result from extreme hyperglycaemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with type 2 diabetes later progress to a state of absolute insulin deficiency (Bennett 1991).

Attachment 6. Protocol Amendment I4L-GH-ABET(a) Summary: A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to Lantus® in Adult Chinese Patients with Type 2 Diabetes Mellitus

Overview

Protocol I4L-GH-ABET has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Estimated first patient visit and last patient visit in synopsis were updated.
- Visit 801 was changed from telephone visit to clinic visit to mitigate the risk of source data inaccuracy.
- For patients who discontinue from the study, completion of Visit 801 was added to avoid missing of Visit 801.
- Tests of fasting serum glucose at Visit 2, Visit 18 or ED were added in study schedule (Attachment 1) as a complementation of self-monitored blood glucose (SMBG) pre-morning value and c-peptide in data interpretation. And in Attachment 2, fasting serum glucose was added.
- For serious adverse events after study completion or patient discontinuation in Section 10.3.1.1, related paragraph was updated according to current protocol template (version 11.0).
- Infuse database is no longer in use, so it was replaced by Clintrial.
- For treatment-emergent adverse event, the definition was revised from events newly reported or worsened after randomizationto those after first study treatment to exclude events occurred or worsened after randomization and prior to first dose. Definition of TEAE in Section 4 was also updated per current clinical protocol template (version 11.0).
- In Attachment 3, estimated sampling for standard laboratory test was updated, and total amount was changed accordingly.
- For hepatic safety monitoring in Section 10.3.3, elevated ALT or AST > 3X ULN or elevated total bilirubin > 2X ULN was changed to elevated ALT or AST ≥ 3X ULN or elevated total bilirubin ≥ 2X ULN.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

2. Synopsis

Length of Study: Estimated first patient visit: Mar 201~~7~~8 Estimated last patient visit: Feb 20~~19~~20

4. Abbreviations and Definitions

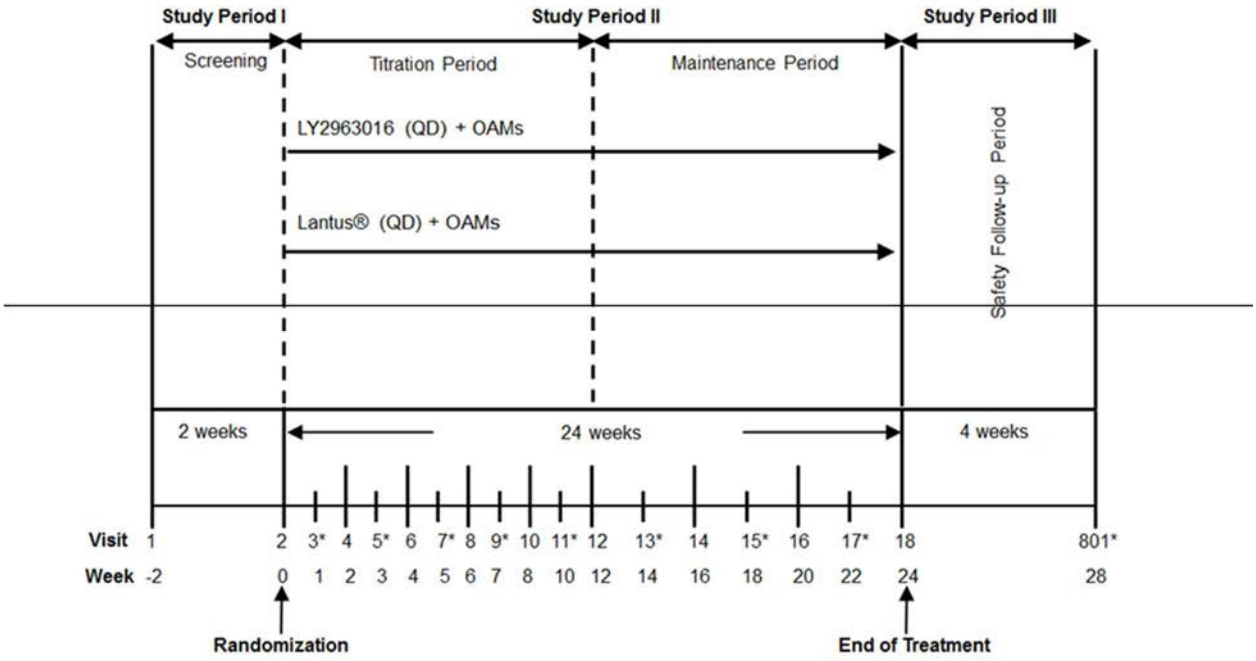
~~**treatment emergent adverse event (TEAE)**~~	~~Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have a causal relationship with this treatment.~~ Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

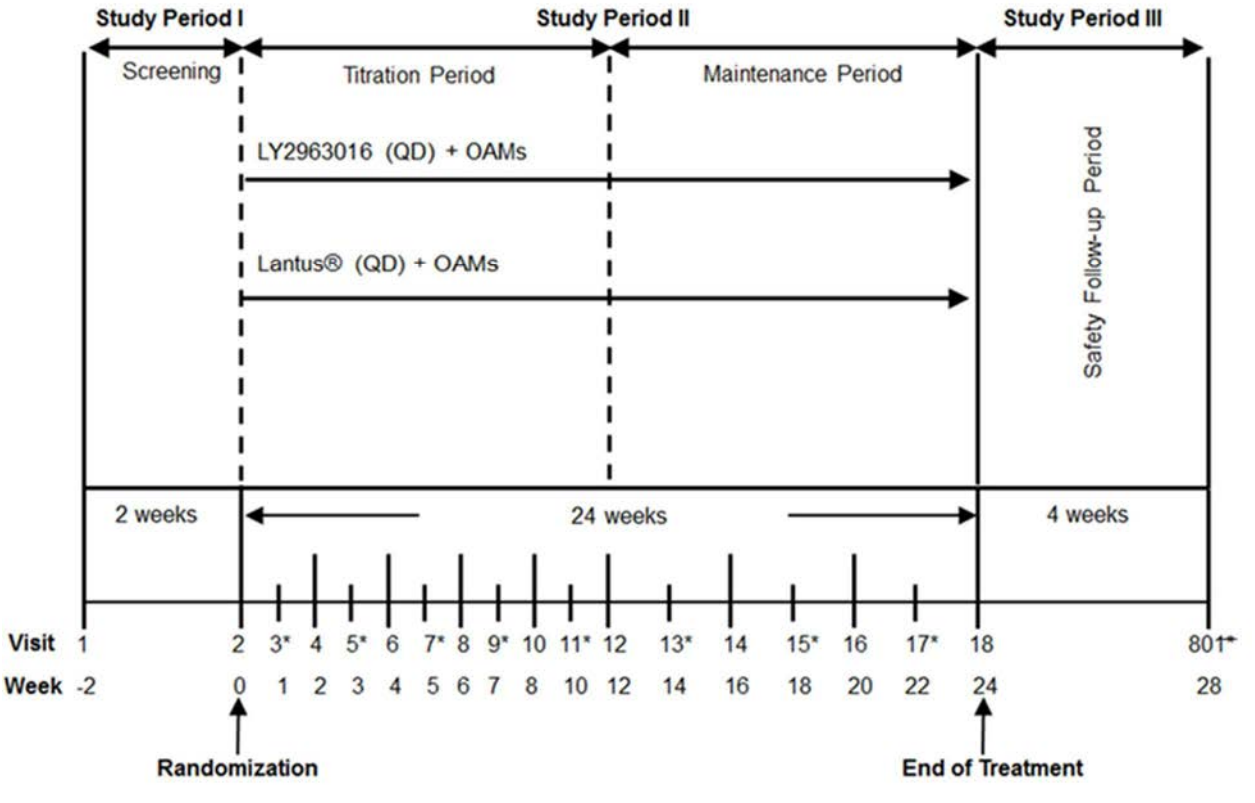
7.1. Summary of Study Design

At approximately 4-week post-treatment endpoint (Visit 801), patients will have a final ~~telephone~~clinic visit at which information will be collected according to the Study Schedule (Attachment 1). The starting dose is 10 units (U), which will be titrated by the weekly dosing algorithm as described in Section 9.5 until fasting blood glucose (FBG) reaches ≤100 mg/dL (5.6 mmol/L) (weekly-base titration till Visit 10 and titration as needed afterwards. The insulin doses can be adjusted between intervals at discretion of the investigators. The titration procedure during the study will occur as described in Section 9.5.

End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.

Figure ABET.7.1 illustrates the study design.





7.2.2.4. Follow-up Visit (Visit 801)

Patients will ~~receive a telephone call~~come to the investigator site approximately 4 weeks after the last treatment visit, at which time information will be discussed and recorded according to the

Study Schedule (Attachment 1). Note: The previous day's insulin dose will be recorded if the patient has continued to take insulin.

Patients who discontinue early from the study will undergo all the end of study procedures and complete Visit 801 as outlined in Attachment 1.

10.3.1.1. Serious Adverse Events

~~The investigator does not need to actively monitor patients for adverse events once the trial has ended, unless provided otherwise in the protocol. However, if an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, the investigator should report the SAEs to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.~~ Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient 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.

10.3.3. Safety Monitoring

If a study patient experiences elevated ALT or AST ~~>~~≥ 3X ULN or elevated total bilirubin ~~>~~≥ 2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 2 and Attachment 4.

10.4.2.1. Nonpharmacogenetic Biomarker Evaluations

This study will employ sample collection. Samples will be collected for nonpharmacogenetic biomarker investigation where local regulations allow. ~~Blood~~Fasting serum samples will be collected at the times specified in the Study Schedule (Attachment 1).

Fasting s~~S~~amples being collected will be used to measure C-peptide to support trial interpretation.

12.2.4. Concomitant Therapy

Concomitant medications, including previous therapies for diabetes, will be summarized by different categories and treatment group using the FAS population. All concomitant therapies that originally mapped using the WHODRUG dictionary in the ~~InFuse~~Clintrial database will be further classified using anatomical, therapeutic chemical code for reporting purpose. Analyses will use test Fisher's Exact Test or Pearson's Chi-square test.

12.2.9.3. Adverse Events

Adverse events will be listed by patient, system organ class, Medical Dictionary for Regulatory Activities® (MedDRA) preferred term, severity, and relationship to the study disease, drug, device, or procedure for all patients. Adverse events will be summarized as treatment-emergent adverse events (TEAEs) for the FAS. Treatment-emergent adverse events are defined as events that are newly reported after first study treatment following randomization, or reported to worsen in severity from ~~randomization~~baseline. The proportion of patients experiencing each TEAE will be presented by preferred term, system organ class, and treatment group. The proportion of patients experiencing each TEAE that are assessed as possibly related to the study disease, drug, device, or procedures will also be summarized. The number and proportion of patients will be presented and compared by treatment using Fisher's exact test or Pearson's chi-square test for the FAS.

Attachment 1. Protocol ABET Study Schedule

	Visit																			
Description of Event	**1**	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10**	**11***	**12**	**13***	**14**	**15***	**16**	**17***	**18**	**801***	**ED#**
Week of Study	-2	0	1	2	3	4	5	6	7	8	10	12	14	16	18	20	22	24	28	
Allowable Deviation (days)[a]	±7		±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±3	±2	±7	
Telephone Visit			x		x		x		x		x		x		x		x		~~x~~	
Clinic Visit	x	x		x		x		x		x		x		x		x		x	x	x
Clinic Assessments																				
Concom Meds[c,d]	x	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[d]	x
Adverse Events[c,d]	x	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[d]	x
Hypoglycemic Episodes[c,d]		x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x	x[d]	x
4-pt SMBG[c,d]			x[c]		x[c]		x[c]		x[c]		x[c]		x[c]		x[c]		x[c]		x[d]	
Study Drug/Device																				
Distribute Study Diary	x	x		x		x		x		x		x		x		x		x		x
Transfer Diary Data to eCRF (InForm™)																				
Insulin Therapy Dose (day prior to visit)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[d]	x
4-pt SMBG[d,i]				x[i]		x[i]		x[i]		x[i]		x[i]		x[i]		x[i]		x[i]	~~x~~[d,i]	x[i]
Lab Assessments[j]																				
Collection of Serum Samples for Biomarkers (Fasting)[d]		x[d]								x[d]								x[d]		x[d]
Fasting Serum Glucose[d]		x[d]																x[d]		x[d]

[#] Patients who discontinue early from the study will complete Visit 801.

[c] Adverse events, hypoglycemic episodes, concomitant medications and the last 3 available profiles of 4-point SMBG reported at telephone visits should be recorded on the eCRF at the next office visit~~, or at Visit 801~~. The 4 points are: before morning, mid-day, and evening meals, and at bedtime.

[d] ~~Information will be collected during a telephone visit and will be recorded on the eCRF. Site documentation will serve as the source for this telephone visit, as the patient will not be returning the paper diary to the site.~~ The measurements should be done fasting before breakfast.

Attachment 2. Protocol ABET Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Platelets	Direct bilirubin
Neutrophils, Segmented	Indirect bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Blood urea nitrogen (BUN)
	Creatinine
Other	Albumin
Pregnancy test[b]	**Fasting serum glucose**
Hemoglobin A_{1c}[a]	
Anti-Glargine Antibodies[a]	
Serum for Biomarkers Nonpharmacogenetic Biomarkers (C-peptide)	

Attachment 3. Protocol ABET Estimated Sampling Summary

Purpose	Sample Type	Estimated Amount per Sample	Number Samples	Estimated Total Amount
Screening tests[a]	Blood	3 mL	2	6 mL
Standard laboratory tests[a]	Blood	3 mL	~~8~~9	~~24~~27 mL
Immunogenicity samples	Blood	8 mL	5	40 mL
Nonpharmacogenetic biomarkers (C-peptide)	Blood	6 mL	3	18 mL
Total				~~88~~91 mL
Hepatic Monitoring[b]	Blood	-	-	3 - 30 mL