Protocol I4L-GH-ABES(a)

A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog,

LY2963016, to Lantus® in Combination with Mealtime Insulin Lispro in

Adult Chinese Patients with Type 1 Diabetes Mellitus

NCT03338023

Approved Date: 02Mar2017

1. Protocol I4L-GH-ABES(a)
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LY2963016

Phase 3, randomized, multicenter, 2-arm, active-control, open label, parallel, 24-week treatment study to compare LY2963016 and Lantus® with mealtime insulin lispro in adult Chinese patients with type 1 diabetes mellitus, with 4-week post-treatment follow up.

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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 current study is a randomized, multicenter, parallel study to compare LY2963016 and Lantus® in the presence of mealtime lispro in adult Chinese patients with type 1 diabetes mellitus (T1DM). This is a 24-week treatment study with a 4-week post-treatment follow up.

Clinical Protocol Synopsis: Study I4L-GH-ABES

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 Combination with Mealtime Insulin Lispro in Adult Chinese Patients with Type 1 Diabetes Mellitus

Number of Planned Patients/Subjects:
  Entered: 330
  Enrolled/Randomized: 258
  Completed: 218
	Phase of Development: Phase 3

Length of Study: Estimated first patient visit: Mar 2018   Estimated last patient visit: Sep 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 margin of 0.40%, as measured by change in hemoglobin A1c (HbA1c) from baseline to 24 weeks, when used in combination with premeal insulin lispro thrice a day (TID) in adult Chinese patients with T1DM.
 	
 The secondary objectives of the study are:
 • To test the hypothesis that Lantus® is noninferior to LY2963016, as measured by change in HbA1c from baseline to 24 weeks, when used in combination with premeal insulin lispro TID (this secondary objectives is tested with a gated approach)
 • To compare the safety of LY2963016 to Lantus® (proportion of patients with detectable anti-glargine antibodies, hypoglycemia and injection site reaction) when used in combination with premeal insulin lispro
 • To compare change in HbA1c at 6, 12, and 18 weeks between LY2963016 and Lantus® when used in combination with premeal insulin lispro
 • To compare 7-point self-monitored blood glucose (SMBG) profiles at baseline, 2, 4, 6, 12, 18, and 24 weeks between LY2963016 and Lantus® when used in combination with premeal insulin lispro
 • To compare percentage of patients with HbA1c <7% and percentage of patients with HbA1c ≤6.5% at 6, 12, 18, and 24 weeks between LY2963016 and Lantus® when used in combination with premeal insulin lispro
 • To compare LY2963016 to Lantus® when used in combination with premeal insulin lispro with regard to the following measures
    o intrapatient blood glucose (BG) variability
    o basal and prandial insulin dose
    o weight change
 • To compare patient-reported outcomes (PRO), as measured by responses to the Insulin Treatment Satisfaction Questionnaire (ITSQ), between LY2963016 and Lantus®

Study Design: A Phase 3, prospective, randomized, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study in patients with T1DM, with a 4-week post-treatment follow up.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Patients with T1DM for ≥1 year, of ≥18 years of age, with a body mass index (BMI) ≤35 kg/m² will be included in the study. Patients should have an HbA1c ≤11%. Patients must be administered with basal-bolus or premixed insulins before enrollment for at least 3 months (90 days) prior to Visit 1. For basal-bolus therapy, bolus insulin includes mealtime injections of human regular insulin, or insulin analog lispro, or aspart, or glulisine; basal insulin can be QD injection of Lantus®, or either QD or twice daily (BID) injection of human insulin isophane suspension [NPH] or detemir. For those patients with premixed therapy before the study, insulin regimens with any NPH/neutral protamine lispro [NPL] (basal) and bolus combination are administered at least BID.

Patients with known hypersensitivity or allergy to the study insulin (Lantus® or insulin lispro) or their excipients, or with significant renal, cardiac, gastrointestinal, or liver disease, will be excluded. Patients with active cancer or cancer within the past 5 years will be excluded. Twice-daily insulin glargine within 6 months prior to Visit 1 will be excluded.

Investigational Product, Dosage, and Mode of Administration or Intervention:

In the patients who were administered with basal-bolus therapies before enrollment with QD basal insulin and mealtime insulins, QD LY2963016 will be started at the same dose as the QD prestudy basal insulin. For those patients with BID prestudy basal insulin as part of basal-bolus regimen, the total daily prestudy basal insulin dose will be reduced by 20% at randomization to LY2963016, therefore, the study basal insulin dose will be 80% of the prestudy basal insulin dose. Insulin lispro will be administered with meals at the same dose as the patient's prestudy mealtime insulin dose while avoiding hypoglycemia, as determined by unit-to-unit conversion.

In the patients who were administered with pre-mixed insulin, the total daily dosage at randomization will be the average for the sum of all insulin doses taken in the 3 days prior to randomization. The total daily dosage will then be split between basal and bolus insulin doses at the discretion of the investigator. The initial basal insulin dose is recommended to be approximately 40% to 60% of the total daily dose. Then the initial bolus insulin dose (insulin lispro, 60% to 40% of the total daily dose) will be divided into 3 equal doses before 3 meals. The doses of initial bolus insulin can be adjusted at the discretion of investigators based on consideration of individual patient's diet/physical activity/or insulin needs as reflected by SMBG pattern.

The basal and bolus insulin dose will be adjusted during the study to achieve glycemic targets (HbA1c <7%, preprandial capillary BGs 79 to 126 mg/dL [4.4 to 7.0 mmol/L], avoiding hypoglycemia). The mode of administration will be subcutaneous.

Planned Duration of Treatment:

Lead-in period: None
Treatment period: 24 weeks when primary outcome will be measured by change in HbA1c from baseline.
Washout period: None
Observation period: 4-week post-treatment follow up

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention:

The initial doses of insulin lispro and Lantus® will be based on the individual patient's prestudy insulin dose/regimen and similarly determined as those for the bolus and basal insulins respectively of the investigational group.

Criteria for Evaluation:

Efficacy:
Primary Endpoint:
Change in HbA1c from baseline to 24 weeks.

Secondary Endpoints:
- 7-point SMBG (expressed as plasma-equivalent glucose values obtained before each meal, after morning meal, after midday meal, at bedtime, and at 3 am).

- Intrapatient variability, as measured by the standard deviation of the 7-point SMBG.
- Change in HbA1c from baseline to 6, 12, and 18 weeks or last observation carried forward (LOCF).
- Percentage of patients with HbA1c <7%, percentage of patients with HbA1c ≤6.5%.
- Total insulin, basal insulin, and mealtime insulin lispro doses in U/day and U/kg/day
- Weight change.
- Patient-reported outcomes, as reflected in responses to Insulin Treatment Satisfaction Questionnaire (ITSQ).

Safety:

Anti-glargine antibodies, laboratory measures, adverse events (AEs; including injection-site reactions and neoplasms), and hypoglycemia will be collected, captured, and/or monitored for safety. Episodes of severe hypoglycemia will be captured as serious adverse events (SAEs).

Hypoglycemia is defined as an event associated with signs or symptoms consistent with hypoglycemia, and/or a BG level ≤70 mg/dL (≤3.9 mmol/L) is noted even if it is not associated with signs or symptoms.

Nocturnal hypoglycemia is defined as any hypoglycemic event that occurs between bedtime and waking.

Severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

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), 109 completers per arm (218 total) are needed at 24 weeks. This calculation assumes no treatment difference in HbA1c between LY2963016 and Lantus®, a common standard deviation (SD) of 1.05% for change from baseline in HbA1c, a two-sided significance level of 0.05, and over 80% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients is 129 per arm (258 total).

Blinded sample-size reestimation may be performed when approximately 40% of the subjects have been enrolled in the study and finished 24-week of treatment, or about 6 months prior to the completion of enrollment, depending on which occur first by team assessment.

Statistical:

The primary efficacy outcome is 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®), stratification factors screening HbA1c Stratum, prestudy treatment, and prestudy metformin or acarbose usage (metformin only, acarbose only, or 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 with the same MMRM model on per-protocol (PP) population and with 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.

A single interim analysis on both efficacy and safety data may be performed to allow interaction with regulatory authorities. Analyses on both interim and final data will be performed using the same statistical methods as described in this protocol and the statistical analysis plan. The study will not stop for early efficacy at the interim analysis therefore no adjustment of Type I error is needed. If there are significant safety concerns arising from the interim analyses, the study team may decide to stop the trial early for safety concerns. The study team will decide, based on the trial operation and blinded safety information, whether and when the interim analyses will be performed.

The final database lock for this study will be performed when all randomized patients have completed (or discontinued from) the study.

If any other unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist will be consulted to determine whether it is necessary to amend the protocol.

3. Table of Contents

A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog, LY2963016, to Lantus® in Combination with Mealtime Insulin Lispro in Adult Chinese Patients with Type 1 Diabetes Mellitus

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4. Abbreviations and Definitions

Term	Definition
ACS	American Cancer Society
ADA	American Diabetes Association
AE (adverse event)	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
BID	twice daily
BMI	body mass index
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.
CRF (case report form) and eCRF (electronic case report form)	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.
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
DCCT	The Diabetes Control and Complications Research Group
ECG	electrocardiogram
ED	early discontinuation
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
EGFR	estimated glomerular filtration rate
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.
FAS	full analysis set
FBG	fasting blood glucose
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
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.
IRB/ERB (institutional review board/ethical review board)	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.
ITSQ	Insulin Treatment Satisfaction Questionnaire

LY2963016

ITT (intent[ion] to treat)	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.
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	human insulin isophane suspension
NPL	neutral protamine lispro
OAM	oral antihyperglycemic medication
OM	observed margins
patient	A study participant who has the disease or condition for which the investigational product is targeted.
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 randomized in the trial are those who have been assigned to a treatment.
rDNA	recombinant deoxyribonucleic acid
SAE	serious adverse event
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
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.

SUSARS (suspected unexpected serious adverse reactions)	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.
TID	thrice a day
T1DM	type 1 diabetes mellitus
TDID	total daily insulin dose
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 Combination with Mealtime Insulin Lispro in Adult Chinese Patients with Type 1 Diabetes Mellitus

5. Introduction

The Diabetes Control and Complications Trial (DCCT) has shown that intensive insulin therapy (3 or more insulin injections or continuous subcutaneous insulin infusion) is a key part of therapy for patients with type 1 diabetes mellitus (T1DM) to improve glycemia and achieve better outcomes (The DCCT Research Group 1993; Nathan et al. 2005). At the time of the DCCT, intermediate- and short-acting human insulins were used, and, despite improved microvascular outcomes, there was a high rate of severe hypoglycemia (62 episodes/100 patient-years) (ADA 2011). Insulin analogs that better mimic the physiologic pattern of mealtime or basal insulin secretion have been developed and shown to be associated with less hypoglycemia with similar glycemic control in patients with T1DM (DeWitt and Hirsch 2003). The American Diabetes Association (ADA) recommends use of insulin analogs as a component of therapy for many patients with T1DM, especially if hypoglycemia is a problem (ADA 2011).

Lantus® (insulin glargine [recombinant deoxyribonucleic acid (rDNA) origin]; [Sanofi- Aventis, Bridgewater, New Jersey, USA]) differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine, and 2 arginines are added to the C-terminus of the B-chain. These changes shift the isoelectric point, producing a solution that is completely soluble at pH 4. When injected into the subcutaneous tissue, the acidic solution is neutralized. This leads to the formation of microprecipitates, from which small amounts of 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). In patients with T1DM, insulin glargine has been shown to provide similar glycemic control to human insulin isophane suspension (NPH), with less or no difference in occurrence of hypoglycemia (Raskin et al. 2000; Ratner et al. 2000).

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-ABEB was a Phase 3, open-label, 52 weeks trial to compare LY2963016 to Lantus® in combination with mealtime insulin lispro in adult patients with T1DM. Severe hypoglycemia was the most frequently reported serious adverse event (SAE) in both groups (LY2963016: 13 patients [4.9%]; Lantus®: 12 patients [4.5%]). LY2963016 and Lantus® were considered to have equivalent efficacy. LY2963016 was safe and well tolerated. The safety profiles for LY2963016 and Lantus® were similar; there were no new safety findings in either treatment group. Both LY2963016 and Lantus®, when used in combination with lispro, provided effective (and similar) glucose control with similar safety profiles. 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 T1DM in combination with insulin lispro, with an efficacy and safety profile similar to that of Lantus® (insulin glargine).

In this randomized, controlled trial, the efficacy and safety of LY2963016 will be compared to Lantus® when used as QD basal insulin in combination with mealtime lispro in adult Chinese patients with T1DM. This study will expand the evaluation of the efficacy and safety of LY2963016 to a broader race/ethnic spectrum of patients with T1DM considering that the study population in Study ABEB was predominantly white (74.5%).

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 detailed 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 will be assessed by the sponsor in aggregate periodically during the course of the study and 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 QD is noninferior to Lantus[®] 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 premeal insulin lispro administered thrice a day (TID).

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To test the hypothesis that Lantus® is noninferior to LY2963016, as measured by change in HbA1c from baseline to 24 weeks, when used in combination with premeal insulin lispro (TID) (this secondary objective is tested with a gated approach).

- To compare the safety of LY2963016 to Lantus® (proportion of patients with detectable of anti-glargine antibodies, hypoglycemia and injection site reaction) when used in combination with premeal insulin lispro.

- To compare change in HbA1c at 6, 12, and 18 weeks between LY2963016 and Lantus® when used in combination with premeal insulin lispro

- To compare 7-point self-monitored blood glucose (SMBG) profiles at baseline, 2, 4, 6, 12, 18, and 24 weeks between LY2963016 and Lantus® when used in combination with premeal insulin lispro

- To compare percentage of patients with HbA1c <7% and percentage of patients with HbA1c ≤6.5% at 6, 12, 18, and 24 weeks between LY2963016 and Lantus® when used in combination with premeal insulin lispro

- To compare LY2963016 to Lantus® when used in combination with premeal insulin lispro with regard to the following measures
    - intrapatient blood glucose (BG) variability
    - basal and prandial insulin dose
    - weight change
- To compare patient-reported outcomes (PRO) between LY2963016 and Lantus® as measured by responses to the Insulin Treatment Satisfaction Questionnaire (ITSQ).

7. Investigational Plan

7.1. Summary of Study Design

Study I4L-GH-ABES (ABES) is a prospective, Phase 3, randomized, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study in patients with T1DM with 4-week post-treatment follow up. The study is designed to determine non-inferiority of LY2963016 to Lantus® in change in HbA1c from baseline in patients with T1DM. Patients will be screened at Visit 1, and eligible patients will be randomized to LY2963016 or Lantus® at Visit 2 to be treated for a total period of 24 weeks.

Patients must be administered with basal-bolus regimen or premixed insulins regimen before enrollment for at least 3 months (90 days) prior to Visit 1. For those patients with basal-bolus therapy before the study, bolus insulin includes mealtime injections of human regular insulin, or insulin analog lispro, or aspart, or glulisine; basal insulin can be QD injection of Lantus®, or either QD or twice daily (BID) injection of NPH or detemir. Twice-daily insulin glargine within 6 months prior to Visit 1 will be excluded. For those patients with premixed therapy before the study, insulin regimens with any basal and bolus combination are administered at least BID.

At randomization, in the patients who were administered with basal-bolus therapies before enrollment with QD basal insulin and mealtime insulins, QD LY2963016 will be started at the same doses as the QD prestudy basal insulin. For those patients with BID prestudy basal insulin, the total daily prestudy basal insulin dose will be reduced by 20% at randomization to LY2963016 or insulin glargine (Product Information for Lantus®, 2007), therefore, the study basal insulin dose will be 80% of the prestudy basal insulin dose. Insulin lispro will be administered with meals at the same doses as the patient's prestudy mealtime insulin dose while avoiding hypoglycemia, as determined by unit-to-unit conversion.

In the patients who were administered with pre-mixed insulin, the total daily dosage at randomization will be the average for the sum of all insulin doses taken in the 3 days prior to randomization. The total daily dosage will then be split between basal and bolus insulin doses at the discretion of the investigator. The initial basal insulin dose is recommended to be approximately 40% to 60% of the total daily dose (Retnakaran and Zinman 2010). Then the initial bolus insulin dose (insulin lispro, 60% to 40% of the total daily dose) will be divided into 3 equal doses before 3 meals. The doses of initial bolus insulin can be adjusted at the discretion of investigators based on consideration of individual patient's diet/physical activity/or insulin needs as reflected by SMBG pattern.

A total of 258 patients are planned to be enrolled in the study, with a target of 218 patients completing the study. Patients will be screened at Visit 1, and eligible patients will be randomized at Visit 2 to receive LY2963016 or Lantus® QD with premeal insulin lispro for a period of 24 weeks, at which time the efficacy endpoint of change in HbA1c levels from baseline will be assessed.

Patients will come to the investigator site for Visits 2, 4, 6, 8, 11, 12, 13, and 801 for various study assessments during the treatment period. Patients will be contacted over the telephone for

Visits 3, 5, 7, 9, and 10 (described as "Telephone Visits" in Section 7.2.2.3) to assess their response to study drug (including 4-point SMBG, AEs, and hypoglycemia) and/or to further adjust insulin doses, if needed. Insulin dose adjustments will be done in both treatment arms to help patients achieve glycemic targets (HbA1c <7%, preprandial capillary BGs 79 to 126 mg/dL [4.4 to 7.0 mmol/L]) while minimizing/avoiding hypoglycemia. Patients will come for a clinic visit at Visit 13 for their final assessments at the completion of 24 weeks. At approximately 4-weeks post-treatment endpoint, patients will have a final clinic visit (Visit 801), at which information will be collected according to the Study Schedule (Attachment 1).

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 ABES.7.1 illustrates the study design.
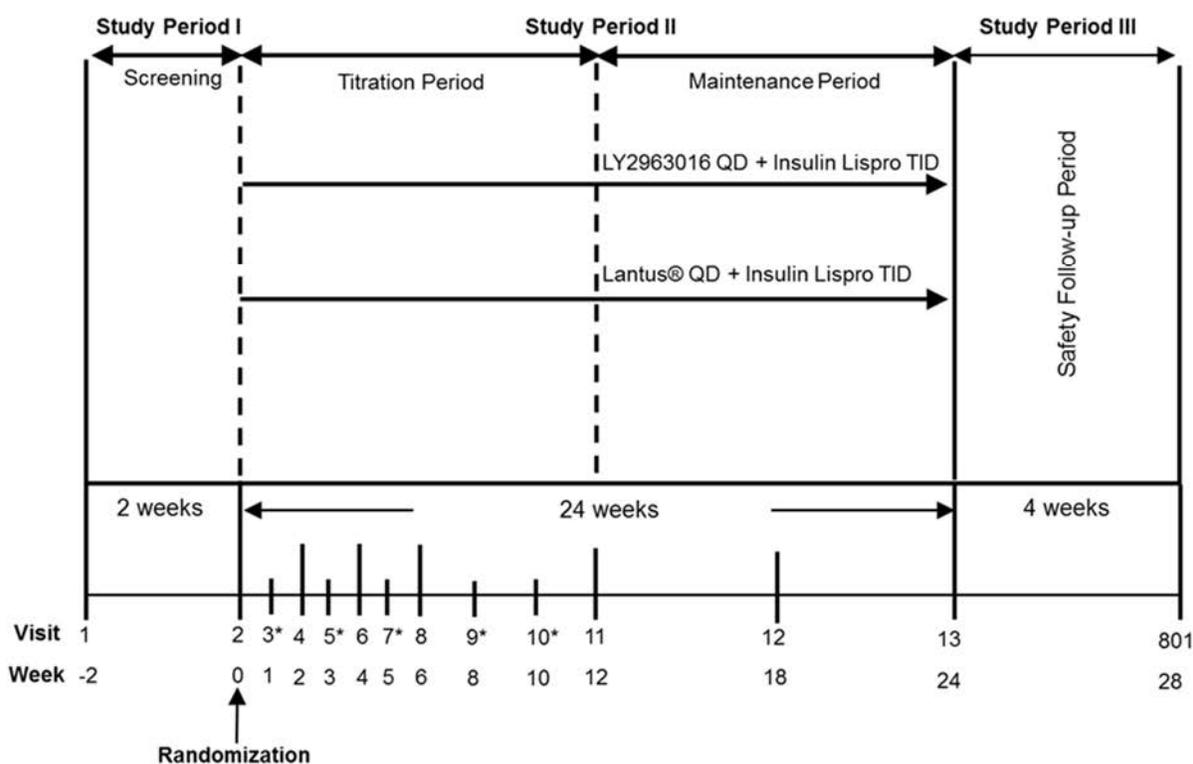
Abbreviations: QD = once-daily administration; TID = thrice-daily administration; * = telephone visit.

Figure ABES.7.1. **Study design for Clinical Protocol I4L-GH-ABES.**

7.2. Discussion of Design and Control

7.2.1. Introduction

The present study is a prospective, Phase 3, randomized, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study in patients with T1DM on basal-bolus insulin

therapy, followed by a 4-week post-treatment follow-up. The trial is designed to allow a head-to-head comparison of the efficacy and safety of 2 basal insulin analogs with the same primary amino acid sequence (LY2963016 and Lantus®) in patients with T1DM. The study design includes screening, randomization, treatment (24 weeks until primary endpoint assessment) and post-treatment follow-up periods. The Treatment Period is composed of a Titration Period and a Maintenance Period. It is expected that most of the basal and bolus insulin dose adjustments should occur during the initial titration period (Week 0 through Week 6); however, titration could extend up to Week 12 for patients who need more intensification to achieve glycemic targets. It is expected that insulin dose adjustments during the Maintenance Period 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 will receive a patient number. The medical history and preexisting conditions, previous insulin exposure, physical examination, height, weight, vital signs, electrocardiogram (ECG) readings, concomitant medications, and adverse events will be recorded during this visit. Laboratory assessments will be performed to determine the eligibility of patients and to include pregnancy tests for women of child-bearing potential (performed at a central laboratory). The HbA1c, hematology and serum chemistry assays will be performed at a central laboratory (Attachment 1 and Attachment 2). 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 will be trained on its use in monitoring their BG levels during the study (Section 7.2.3), including instructions on obtaining the 7-point SMBG profiles that will be collected at Visit 2. Qualified medical staff will instruct patients about signs and symptoms of hypoglycemia and hyperglycemia and how to manage them. Patients will be provided study diaries and training to properly use the study diary at Visit 1 for recording BG values, corresponding insulin doses, hypoglycemic episodes, any AEs, and concomitant medications taken during the study (Attachment 1). If allowed by local law, patients may keep the study-provided blood glucose meter at the end of their study participation.

Patients who do not meet all the inclusion criteria at Visit 1 will be considered screen failures. As the patient's eligibility for randomization may not be known at Visit 1 (for example, given that results of laboratory tests may not be available), the site could either provide a tentative schedule for Visit 2 or arrange for follow up with the patient to confirm eligibility, and then prepare for and schedule Visit 2 as they deem appropriate and efficient.

7.2.2.2. Randomization (Visit 2)

7.2.2.2.1. Patients Eligible for Randomization at Visit 2
At Visit 2, additional clinical assessments will occur, as outlined in the Study Schedule (Attachment 1). More specifically, the following activities will also occur at this visit:

- Eligible patients will be randomized to 1 of 2 treatment groups by a random assignment based on Visit 1 HbA1c, prestudy treatment with basal-bolus insulin or premixed insulin, and prestudy metformin or acarbose usage (metformin only, acarbose only, or neither). For patients with prestudy treatment of metformin or acarbose (excluding those taken both) prior to Visit 1, their concomitant OAM will be discontinued at Visit 2.

- Study material (study insulins, diary, and blood glucose monitoring supplies) will be dispensed or distributed at Visit 2 as indicated in the Study Schedule (Attachment 1).

- Study personnel will train patients on insulin pen injector use and proper injection technique, SMBG levels (Section 7.2.3), and proper use of the study diary for recording AEs, BG values and corresponding insulin doses, and hypoglycemia recognition and management.

- Patients also will be instructed about diet and physical activity and encouraged to maintain healthful habits of diet/activity throughout the study.

- Study diaries from Visit 1 will be collected, and patients will be given a study diary at Visit 2 and each subsequent investigator-site visit. The diaries will be source documents for the patients with records of 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 will be used by the investigator to determine any dose adjustments needed for a patient. As indicated in the Study Schedule (Attachment 1), baseline 7-point SMBG profiles will also be reviewed and transferred to an electronic case report form (eCRF).

- Patient safety will be assessed, including body weight, vital signs, use of concomitant medications, and any AEs or hypoglycemic episodes that occurred since Visit 1.

- A blood sample will be drawn to determine the baseline HbA1c level. Blood samples will be drawn during Visit 2 for immunogenicity tests and biomarker detection (as warranted) (Section 10.4.2). Patients will be administered questionnaires (ITSQ) to assess PROs at baseline with regard to insulin treatment satisfaction.

7.2.2.2.1.1. Instructions for Insulin Self-administration
Patients will administer their basal insulin QD dose subcutaneously (in the abdomen, upper arm, or thigh) at any time of the day approximately the same time every day from the following day after Visit 2. 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 before the first injections (Visit 2).

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. Telephone Visits

Between each investigator-site visit, patients will have a telephone visit with the investigator or designee at Visit 3, 5, 7, 9, and 10.

The main purpose of telephone visits is to check SMBG values and ensure that patients are administering the appropriate insulin dose. Because the study diaries are considered to be source documents, applicable data from telephone visits will be included and entered in the eCRF from the patient diary as part of the next office visit.

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

- Blood glucose readings from the 4-point SMBG from 3 separate days (preferably most recent readings) (Attachment 1) during the period prior to each telephone visit will be noted (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 those values have been correlated with the study diary values.
- Hypoglycemic episodes since last visit.
- The previous day's insulin dose.
- Any AEs experienced, including any injection-site skin reactions, and any changes in medications since last visit
- Titration of insulin/insulin dose adjustment, if indicated based on above (see also Attachment 5).
- Reeducation of the patient as needed.
- Preparation for next office visit.

Patients will retrieve information about BG values and hypoglycemic episodes from entries in their study diaries. Telephone visits can also be conducted as informal office visits at the study site if more practical. Although 5 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.

7.2.2.4. Study Visits (Visit 3 to Visit 13 or Early Discontinuation)

Patients will come to the investigator site at 2-week intervals between Visit 2 and Visit 8. From Visit 8 to Visit 13, patients will come to the clinic at 6-week intervals. Visit 801 is a 4-week follow-up clinic visit (Attachment 1).

Between Visit 2 and Visit 4 and Visit 4 and Visit 6, Visit 6 and Visit 8, Visit 8 and Visit 11, there are telephone visits (Visits 3, 5, 7, 9 and Visit 10), which are described separately (Section 7.2.2.3).

The following activities will occur during Visits 3 to Visit 13 or Early Discontinuation (ED):

- study diaries collected and reviewed for BG levels, episodes of hypoglycemia, injection-site skin reactions, and insulin self-administration (Section 7.2.2.2.1.1)

- distribute study diaries (not completed at ED)

- dispense glucose-meter supplies as needed (not completed at ED)

- dispense study drug/device at Visits 8, 11, and 12 (not completed at Visit 13 or at ED)

- collection of blood sample for HbA1c assessment to determine efficacy of treatment values for each patient at Visits 8, 11, 12, and Visit 13 (or ED)

- transfer data from study diaries into eCRF (including previous day's insulin dose from last telephone visit)

- collect study drug at Visits 8, 11, 12, and Visit 13 (or ED)

- the previous day's insulin dose

- titration of insulin/adjust insulin dose as needed during visits (See Attachment 5; not completed at Visit 13 or at ED)

- assessment of vital signs and body weight

- blood sampling for chemistry and hematology at Visit 13 or ED

- inquiries of AEs

- inquire about use of concomitant medications

- collection of blood sample to determine generation of anti-glargine antibodies at Visits 4, 8, 11, and Visit 13 (or ED)

- collection of serum samples for biomarker analyses during Visit 8 and Visit 13

- Health outcomes of the study will be measured as reflected in responses to ITSQ administered to the patients during Visit 13, (or ED), as indicated in the Study Schedule (Attachment 1).

In addition to the daily BG monitoring, patients will be required to complete the following, which are reviewed and/or transferred to eCRF during Visit 3 to Visit 13 or ED:

- 7-point SMBG profiles (described in Section 7.2.3) on 2 separate days in the 1-week period prior to all investigator-site visits (or at ED) (preferably most recent readings).

- 4-point SMBG values (once before each meal and at bedtime, recorded before and reviewed during the telephone visit period) will be recorded in the eCRF during the next investigator-site visit.

Study treatment will be discontinued at Visit 13 if not discontinued beforehand, after which an appropriate diabetes treatment regimen will be initiated by the investigator or the patient's treating physician in accordance with local standards of care.

7.2.2.5. 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). Patients who discontinue early from the study will undergo all end-of-study procedures and complete Visit 801 as outlined in Attachment 1. These data will be collected and stored for future reference/analyses, if needed.

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.

Throughout the study, patients will be expected to check their fasting blood glucose (FBG) values daily to assess the need for basal insulin-dose adjustments (Attachment 5). They will also be instructed to record results of 4- and 7-point SMBG values in the study diaries, as described below, so they can be shared and help inform the investigators who will direct insulin-dose adjustments, as needed, to help patients achieve glycemic targets (HbA1c <7%, preprandial BG 79 to 126 mg/dL [4.4 to 7.0 mmol/L]) while minimizing/avoiding hypoglycemia. For consistency, the first recorded BG value for each profile should be a premorning meal value followed by the other specified BG values throughout the day.

- Patients will be instructed to complete 3 separate 4-point SMBG values (once before each meal and at bedtime) (preferably most recent readings) during the period prior to each telephone visits. Four-point SMBG values will be reported during telephone visits and will be recorded at the subsequent office visit or Visit 801.

- Patients will be instructed to complete 2 separate 7-point SMBG profiles in the 1-week period prior to each office visit from Visit 2 to Visit 13 (or at ED) (preferably most recent readings). At Visit 801, only 4-point SMBG is required to be collected. The SMBG profiles will consist of:

  - before the morning meal, midday meal, and evening meal; 2-hour postprandial measurements for the morning, midday meal, at bedtime and 3 am.

Throughout the study, patients will be expected to routinely check their fasting, premeal, and bedtime BG values daily to help assess the need for dose adjustments and to guide dosing of the mealtime/fast-acting insulin lispro (Attachment 5). Patients may be requested by investigators (as they deem necessary) to perform more intensive self-monitoring, if clinically indicated. Both 4-point and 7-point SMBG values will be recorded in the diaries and transcribed into the eCRF at the office visit (Attachment 1 and Attachment 5).

Missing values in SMBG profiles will not be considered protocol deviations unless, in the opinion of the investigator, they reflect noncompliance with the protocol.

8. Study Population

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 T1DM based on the disease diagnostic criteria (World Health Organization [WHO] Classification) (Attachment 6).

[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] Aged ≥18 years.

[4] Have duration of T1DM ≥1 year.

[5] Have HbA1c ≤11 %.

[6] Have been administered with basal-bolus insulins or pre-mixed insulins for at least 90 days prior to Visit 1 (see also Exclusion Criterion [33]):

- for those patients with basal-bolus therapies, bolus insulin includes mealtime injections of human regular insulin, or insulin analog lispro, aspart, or glulisine; basal insulin can be QD injection of Lantus®, either QD or BID injection of NPH or detemir.

- for those patients with premixed insulin, insulin regimens with any NPH/NPL[neutral protamine lispro] (basal) and bolus combination are administered at least BID.

[7] Have a body mass index (BMI) ≤35 kg/m2.

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

o perform SMBG measurements

o complete patient diaries as instructed for this protocol

o use the insulin injection device(s) according to the instructions provided

o be receptive to diabetes education

o comply with the required study insulins and study visits.

[9] 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:

[10] Exposure to an insulin glargine other than Lantus® within previous 30 days.

[11] Excessive insulin resistance at entry into the study (total daily insulin dose [TDID] ≥1.5 units [U]/kg).

[12] Have had more than one episode of severe hypoglycemia, as defined in Section 9.10 of the protocol, within 6 months prior to entry into the study.

[13] Have had more than one episode of diabetic ketoacidosis or emergency room visits for uncontrolled diabetes leading to hospitalization within 6 months prior to entry into the study.

[14] Have known hypersensitivity or allergy to any of the study insulins (Lantus® or insulin lispro) or to excipients of the study insulins.

[15] Are pregnant, 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.

[16] Women who are breastfeeding.

[17] Have taken any oral antihyperglycemic medications (OAMs) within 3 months prior to Visit 1. Except for those patients with metformin or acarbose at a stable dose for more than 90 days prior to Visit 1 (excluding those taken both), their concomitant OAM will be discontinued at randomization before the study treatment.

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

[19] Have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.

[20] Have received treatment with pramlintide or with continuous subcutaneous insulin infusion within 3 months prior to Visit 1.

[21] Have congestive heart failure Class III and IV.

[22] Have obvious clinical 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.

[23] Have any active cancer, or a personal history of cancer within the previous 5 years (except basal-cell cancer or carcinoma in situ).

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

[25] Have presence of clinically significant gastrointestinal disease (for example, clinically active gastroparesis associated with wide glucose fluctuations).

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

[27] 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.

[28] 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 Addison's disease or adrenal deficiency) or have received such therapy within the 4 weeks immediately preceding Visit 1.

[29] Have an irregular sleep/wake cycle (for example, patients who sleep during the day and work during the night).

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

[31] 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.

[32] Are Lilly and Boehringer Ingelheim employees.

[33] Have previously completed or withdrawn from this study after having signed the ICF.

[34] 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.

[35] Are using BID insulin glargine within 6 months (180 days) prior to Visit 1.

[36] Have evidence of a significant, active, uncontrolled endocrine or autoimmune abnormality, as judged by the investigator.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criterion [10] excludes patients because prior exposure to biosimilar insulin glargine may confound the interpretation of the study endpoints if anti-insulin glargine antibodies are present at baseline.

Exclusion criterion [11] excludes patients who may not have a physiological response to the study treatment, to meet the study objectives.

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

Exclusion criteria [15] and [16] assure the safety of unborn and newborn children.

Exclusion criteria [17], [19], and [20] exclude medications that may cause HbA1c lowering not attributable to the regimens being studied, which could lead to misinterpretation of the results. Additionally, exclusion criterion [17] also precludes patients with unclear diagnosis of T1DM.

Exclusion criterion [18] excludes traditional medicine with anti-hyperglycemic effects due to safety concerns and leading to misinterpretation of the results.

Exclusion criteria [14] and [21 to 27] represent clinical situations that may prevent patients from completing the protocol, influence the effect or safety of study regimens, or are serious conditions that pose a risk for morbidity and mortality. Exclusion criterion [23] 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 [28] relates to the negative effect of steroid therapy on the management of diabetes.

Exclusion criterion [29] avoids a situation where patients would need highly individualized insulin regimens compared to the planned regimen for this study. Their schedule could also confound the results of the 7-point SMBG profiles.

Exclusion criterion [30] permits investigators to exclude patients who meet all other inclusion and exclusion criteria, but may not be appropriate study candidates.

Exclusion criteria [31] and [32] reduce potential bias due to conflict of interest.

Exclusion criterion [33] eliminates the possibility of duplicate participation by a patient.

Exclusion criterion [34] prevents a situation in which potential positive or negative outcomes may not be clearly attributable to the regimens in the study.

Exclusion criterion [35] excludes patients recently administrating twice daily insulin glargine, as the study design involves once-daily treatment with insulin glargine or LY2963016. Switching from twice- to once-daily insulin glargine dosing might not be beneficial to the patient given no guidance provided on twice-daily insulin glargine use in Lantus® label.

Uncontrolled endocrine or autoimmune restriction [36] excludes the clinical situation that may influence the efficacy or safety of study regimens.

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 21] and [23 to 34] is observed or develops after study entry or enrollment. In this case, the patient will be discontinued from the study at the next visit, or sooner if the patient safety is the rationale for the exclusion criterion.

- If the patient is off study medication for more than 10 consecutive days' study, he/she will be discontinued from the study.

- If the investigator determines that the patient is noncompliant and should be discontinued from the study. Patients who discontinue study drug early should have ED procedures performed, as shown in the Study Schedule (Attachment 1). Patients who discontinue after randomization will not be replaced.

- Enrollment 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

    o the investigator decides that the patient should be discontinued from the study

    o 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

    o the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

- Sponsor Decision

    o 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

    o 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 in accordance with the product labeling in China, when applicable. This study involves a comparison of LY2963016 administered QD subcutaneously with Lantus® QD along with thrice premeal insulin lispro to patients with T1DM.

Study treatment will start on the second day of randomization.

At randomization, patients who were administered with basal-bolus therapies before enrollment with QD basal insulin and mealtime insulins will receive instruction to start new regimen with either QD LY2963016 or insulin glargine as basal insulin at the same doses next day. For those patients with BID prestudy basal insulin as part of basal-bolus regimen, the total daily prestudy insulin dose will be reduced by 20% therefore, the study basal insulin dose will be 80% of the prestudy basal insulin dose. Insulin lispro will be administered with meals at the same doses as the patient's prestudy mealtime insulin dose while avoiding hypoglycemia, as determined by unit-to-unit conversion.

In the patients who were administered with premixed insulin will receive instruction to start new regimen on the next day. The total daily dosage of new regimen will be the average for the sum of all insulin doses taken in the 3 days prior to randomization. The total daily dosage will then be split between basal and bolus insulin doses at the discretion of the investigator. For the treatment regimen, the initial basal insulin dose should be approximately 40% to 60% of the total daily dose. Then the initial bolus insulin dose (insulin lispro, 60% to 40% of the total daily dose) will be divided into 3 equal doses before 3 meals. The doses of initial bolus insulin can be adjusted at the discretion of investigators based on consideration of individual patient's diet/physical activity/or insulin needs as reflected by SMBG pattern. This conversion is consistent in the decrease of insulin dose with aforementioned scenario when switching from BID basal to once-daily insulin glargine, but relatively conservative. Physician could opt to use a once-daily basal insulin dose that is 20% less than the total basal insulin dose for the previous premix regimen at their discretion after evaluation of individual patient's clinical conditions.

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
- returning all unused medication to Lilly or its designee at the end of the study

In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has the appropriate facilities and written procedures to dispose of clinical trial materials.

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.

At randomization, patients will be provided with insulin lispro as a prefilled pen injector to be used as premeal insulin. Study insulins (LY2963016, Lantus® and Lispro®) will be supplied by Lilly or its representative, in accordance with current good manufacturing practices (GMP) and will be supplied with lot numbers.

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 by stratified randomization to 1 of the 2 treatment arms, in a ratio of 1:1, via random assignment using the interactive web response system. To achieve between-treatment group comparability, patients will be stratified by screening HbA1c stratum (<8.5%, ≥8.5%), pre-study treatment (Lantus®-bolus, other basal-bolus, premixed insulin), and pre-study metformin or acarbose usage (metformin only, acarbose only, or neither).

9.4. Rationale for Selection of Doses in the Study

As supported by preclinical data demonstrating similar glucodynamics between Lantus® and LY2963016 (data on file), these insulins will be dosed in a similar fashion as described in the protocol (Section 9.5).

For patients whose glycemic control is within desired levels on prestudy insulins, once they are switched from their prestudy insulins to LY2963016 or Lantus® and insulin lispro, the investigators and patients should continue to manage the patient's insulin therapy to effectively maintain glycemic goals (HbA1c <7%, preprandial capillary BGs 79 to 126 mg/dL [4.4 to 7.0 mmol/L], avoiding hypoglycemia). However, for patients with inadequate glycemic control, further insulin titration should be done (in conjunction with patient education, if needed) to improve glycemic control, as guided by general principles of intensive/flexible insulin therapy described below and in Attachment 5.

At randomization, in the patients who were administered with basal-bolus therapies before enrollment, QD LY2963016 will be started at the same doses as the QD prestudy basal insulin. For those patients with BID prestudy basal insulin as part of basal bolus regimen, the total daily prestudy insulin dose will be reduced by 20% at randomization to LY2963016 or insulin glargine, therefore, the study basal insulin dose will be 80% of the prestudy basal insulin dose. Insulin lispro will be administered with meals at the same doses as the patient's prestudy mealtime

insulin dose while avoiding hypoglycemia, as determined by unit-to-unit conversion. Based on the patient's prestudy mealtime insulin regimen relative to his/her lifestyle, the investigator could translate the patient's previous mealtime insulin regimen so that the patient's prestudy mealtime insulin is replaced with a similar dose of insulin lispro to be used during the study. During the course of the study, the patient's mealtime insulin doses will be adjusted and optimized by the investigator. Study participants will administer mealtime insulin doses before meals to provide insulin coverage for the meal, as well as a correction dose if the premeal BG reading is above target.

Thus, a patient consuming 3 main meals will have a TDID consisting of the following:

TDID = basal insulin dose + all mealtime insulin doses (including corrections).

General guidance in determining how doses and any necessary dose adjustments will be made during the study is described in Attachment 5.

In the patients who were administered with premixed insulin, the total daily dosage at randomization will be the average for the sum of all insulin doses taken in the 3 days prior to randomization. The TDID will then be split between basal and bolus insulin doses at the discretion of the investigator. While adjusting the basal and premeal insulins, investigators may be cognizant that balancing the amount of basal and premeal insulin could help attain tighter glycemic control while minimizing hypoglycemia. In general, the TDID for multiple daily insulin injections is distributed to approximately 50% basal and 50% premeal or mealtime insulin (Mecklenburg 1998; Skyler 1998). However, this ratio may vary according to clinical practice. The initial basal insulin dose is recommended to be approximately 40% to 60% of the total daily dose. Then the initial bolus insulin dose (insulin lispro, 60% to 40% of the total daily dose) will be divided into 3 equal doses before 3 meals. The doses of initial bolus insulin can be adjusted at the discretion of investigators based on consideration of individual patient's diet/physical activity/or insulin needs as reflected by SMBG pattern.

The dose of LY2963016 or Lantus® will be titrated primarily based on FBG values, with algorithm-based treat-to-target titration described in Attachment 5. The dosing algorithm can be individualized at the discretion of the investigators due to medical reasons. To ensure that the HbA1c by Week 24 reflects glycemic control on the patient's insulin regimen, most of the adjustments in the basal and bolus doses should be completed during the first 6 weeks of the Titration Period (or, for patients who need more intensification to better achieve glycemic targets, up to 12 weeks). During the Maintenance Period, it is expected that adjustments to insulin dose would be for safety such as hypoglycemia or unacceptable hyperglycemia.

9.5. Selection and Timing of Doses

All treatments will be administered according to the country-specific product labeling where applicable. Insulin lispro should be administered subcutaneously within 15 minutes before meals or immediately after the meal. LY2963016 and Lantus® are to be administered QD by the patients at bedtime or anytime of the day (but approximately the same time of the day) every day from the following day after Visit 2. Investigators are advised to take into account patients'

mealtimes and timing of the BG readings in making adjustment decisions on insulin dose or in requesting additional BG monitoring. For example, if a patient's evening meal is late and bedtime is only an hour later, the investigator should exercise caution in making insulin-dose adjustments to attain glycemic targets and to prevent nocturnal hypoglycemia.

The investigator will guide the patient in adjusting the insulin doses based on the SMBG profiles during the study to achieve preprandial BG targets of 79 to 126 mg/dL (4.4 to 7.0 mmol/L) while minimizing hypoglycemia.

9.5.1. Special Treatment Considerations

There is no plan for rescue therapy in this study.

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, while Lantus®, insulin lispro, and the prestudy basal-bolus insulin therapy insulins are readily available.

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

As described in Exclusion Criteria [10] and [17 to 20] (Section 8.2), patients should not take any other BG-lowering medications 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.

In emergencies, it may be necessary for patients to 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 clinical research scientist. The decision should be documented by a note to the investigator's file.

9.9. Treatment Compliance

The investigator will assess the compliance of the patient at each visit, based on a review of the patient's glycemic control, adherence to the visit and treatment schedule, completion of patient 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. Specific study data will not 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, and treatment 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 ≤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 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 plasma glucose determination but that was presumably caused by a plasma glucose 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 plasma glucose 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, Sample Collection and Testing, 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 Efficacy Measure

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

10.1.2. Secondary Efficacy Measures

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

- change in HbA1c from baseline to 6, 12, and 18 weeks or LOCF

- percentage of patients with HbA1c <7%, and the 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 breakfast and lunch
    - bedtime
    - 3 am

- intrapatient variability as measured by the standard deviation of the 7-point SMBG

- total insulin, basal insulin, and mealtime insulin lispro doses in U/day and U/kg/day

- 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 used to compare the health outcomes for the 2 insulins. This will be reflected in responses to ITSQ administered at baseline (Visit 2) and 24 weeks (Visit 13) or 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 patients 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 (5 items)

- Lifestyle Flexibility (3 items)

- Glycemic Control (3 items)

- Hypoglycemic Control (5 items)

- Satisfaction with the Insulin Delivery Device (6 items)

All individual patient-domain scores will be calculated as the sum of the items in the domain. If an item score is missing for a patient 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 for 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 under treatment in the study.

After the ICF is signed, study-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 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 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

- 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 serious adverse drug events 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 fit 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), then the investigator should select "Other" as the outcome (that is, considered significant by the investigator for a reason other than those specified).

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 the 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 will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP 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 $\geq$ 3X ULN or elevated total bilirubin $\geq$ 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 on 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 reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

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

10.4. 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 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 serum pregnancy test will be analyzed by 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.

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 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 antidrug 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, 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.

LY2963016

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), 109 completers per arm (218 total) are needed at 24 weeks. This calculation assumes no treatment difference in HbA1c between LY2963016 and Lantus®, a common standard deviation (SD) of 1.05% for change from baseline in HbA1c, a two-sided significance level of 0.05, and over 80% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients is 129 per arm (258 total).

Blinded sample-size reestimation may be performed when approximately 40% of the subjects have been enrolled in the study and finished 24-weeks of treatment, or about 6 months prior to the completion of enrollment, depending on which occur first by team assessment. This reestimation will use a statistical model to estimate the variability in the change in HbA1c from baseline to 24 weeks using all available patient HbA1c values at the time of data cutoff. The estimate of variability will then be used to recalculate the sample size that would be needed to have 80% conditional power for a NIM of 0.4%, assuming no difference between treatments. The sample size from the study is constrained by a predefined maximum sample size of 400 patients. If the recalculated sample size is smaller than sample size planned (258), the study will enroll to the sample size planned. If the recalculated sample size is larger than the planned sample size, the team will make a decision whether to increase sample size to the reestimated sample size. If the reestimated sample size is larger than the predefined maximum sample size, the team will increase the sample size to 400 subjects.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

All data will be entered, verified, and archived at 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. Patients are assigned to the treatment arm to which they were randomized.

4. Per-protocol (PP) - patients in the FAS/ITT population who also meet the following criteria:

   a. violate no inclusion or exclusion criteria

   b. have not discontinued from the study prior to 24 weeks

   c. have not been off study medication for more than 10 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 All 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 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 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.

12.2.5. 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 postbaseline visit in HbA1c level as the dependent variable with treatment (LY2963016, Lantus®), pre-study treatment (Lantus®-bolus, other basal-bolus, premixed insulin), and pre-study metformin or acarbose usage (metformin only, acarbose only, or 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, pre-study treatment, and pre-study metformin or acarbose usage (metformin only, acarbose only, or 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 postbaseline 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 postbaseline value.

12.2.7. Secondary Efficacy Outcomes and Methodology

The continuous secondary efficacy outcomes include:

- 7-point SMBG measurements as listed in the Study Schedule (Attachment 1)
    - premeal for each meal
    - postmeal for breakfast and lunch
    - bedtime
    - 3 am
- intrapatient variability as measured by the SD of the 7-point SMBG
- change in HbA1c from baseline to 6, 12, and 18 weeks or LOCF
- total insulin, basal insulin, and mealtime insulin lispro doses in U/day and U/kg/day
- 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 proportions of subjects achieving HbA1c target values (HbA1c <7.0% and ≤6.5%) at any point during the study 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 baseline (Visit 2), prior to randomization and at Week 24 (Visit 13 or ED). Change from baseline to Week 24 or end of study will be analyzed using the ANCOVA model for the FAS population.

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

12.2.9. Safety Analyses

12.2.9.1. Immunogenicity Test

The proportion of patients with detected anti-glargine antibodies will be summarized as counts and percentages at baseline, at Visits 4, 8 and 11, at the 24-week endpoint (last observation carried forward [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. 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 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.

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 both 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.

12.2.9.3. 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 2 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, prestudy treatment, and prestudy metformin or acarbose usage. 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.

12.2.9.4. 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, prestudy treatment, and prestudy metformin or acarbose usage 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.

12.2.9.5. 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 ($<7\%$, $\geq7\%$)

- entry HbA1c levels ($<8.5\%$, $\geq8.5\%$)

- prestudy treatment (Lantus®-bolus, other basal-bolus, premixed insulin)

- entry BMI (<30, ≥30)

- entry age (<65, ≥65)

- Prestudy metformin or acarbose use (metformin only, acarbose only or neither)

- Renal function, as estimated by estimated glomerular filtration rate (EGFR). The following EGFR categories will be used:

  o normal or increased GFR: EGFR (≥90 mL/min/1.73 m^2)

  o mild reduction in GFR: EGFR (60 to 89 mL/min/1.73 m^2)

  o Moderate reduction in GFR: EGFR (30 to 59 mL/min/1.73 m^2)

  o Severe reduction in GFR: EGFR (15 to 29 mL/min/1.73 m^2)

  o Kidney failure: EGFR (<15 mL/min/1.73 m^2).

The change in HbA1c from baseline to 24-week endpoint will be analyzed using MMRM with treatment, visit, prestudy treatment, prestudy metformin or acarbose usage, 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

A single interim analysis on both efficacy and safety data may be performed to allow interaction with regulatory authorities. Analyses on both interim and final data will be performed using the same statistical methods, as described in this protocol and the SAP. The study will not stop for

early efficacy at the interim analysis therefore no adjustment of Type I error is needed. If there are significant safety concerns arising from the interim analyses, the study team may decide to stop the trial early for safety concerns. The study team will decide, based on the trial operation and blinded safety information, whether and when the interim analyses will be performed.

If any unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist 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

13.2. Ethical Review

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). All ICFs must be compliant with the ICH guideline on GCP.

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:

- 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

- applicable ICH GCP Guidelines

- applicable laws and regulations

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

LY2963016

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, may participate as investigators in this clinical trial.

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 CSR accurately describes the conduct and results of the study.

14. References

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Attachment 1. Protocol ABES Study Schedule

Study Schedule, Protocol I4L-GH-ABES

Description of Event								Visit							
	1	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10***	**11**	**12**	**13**	**801**	**ED#**
Week of Study	-2	0	1	2	3	4	5	6	8	10	12	18	24	28	
Allowable Deviation (Days)[a]	±7[a]		±2[a]	±3[a]	±3[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	
Telephone Visit			X		X		X		X	X					
Clinic Visit	X	X		X		X		X			X	X	X	X	X
Screen Inclusion															
Screening	X														
Informed Consent Obtained	X														
Patient Number Assigned	X														
Randomization		X													
Clinic Assessments															
Medical History and Pre-existing Conditions	X														
Previous Insulin Exposure	X														
Physical Exam	X														
Height	X														
Weight	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
Concom. Meds[b]	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X[b]	X	X	X	X	X
Adverse Events[b]	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X[b]	X	X	X	X	X
Hypoglycemic Episodes[b]		X	X[b]	X	X[b]	X	X[b]	X	X[b]	X[b]	X	X	X	X	X
7-point SMBG Profile[c]		X[c]		X[c]		X[c]		X[c]			X[c]	X[c]	X[c]		X[c]
4-point SMBG[b]			X[b]		X[b]		X[b]		X[b]	X[b]				X	

Description of Event	Visit														
	1	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10***	**11**	**12**	**13**	**801**	**ED#**
Week of Study	-2	0	1	2	3	4	5	6	8	10	12	18	24	28	
Allowable Deviation (Days)a	±7a		±2a	±3a	±3a	±7a	±7a	±7a	±7a	±7a	±7a	±7a	±7a	±7a	
Telephone Visit			X		X		X		X	X					
Clinic Visit	X	X		X		X		X			X	X	X	X	X
Study Drug/Device/Training and Educationd															
Dispense Glucose Meter and Suppliese	X	Xe		Xe		Xe		Xe			Xe	Xe	Xe		
Glucometer Training	X														
Dispense Study Drug/Device		X						X			X	X			
Injection Technique/Device use training		X													
Training on Signs/Symptoms of Hypo/hyperglycemia	X														
BG Level Monitoring Training	X	X													
Diet and Exercise Counseling		X													
Distribute Study Diary	X	X		X		X		X			X	X	X		X
Diary Use Training	X	X													
Adjust Insulin Dose (if Applicable)			X	X	X	X	X	X	X	X	X	X			
Collect Study Drug								X			X	X	X		X
Collect Study Diaryf		Xf		Xf		Xf		Xf			Xf	Xf	Xf		Xf
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
7-point SMBG Profilec,g		Xc		Xc		Xc		Xc			Xc	Xc	Xc		Xg

Description of Event															
	Visit														
Description of Event	**1**	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10***	**11**	**12**	**13**	**801**	**ED[#]**
Week of Study	-2	0	1	2	3	4	5	6	8	10	12	18	24	28	
Allowable Deviation (Days)[a]	±7[a]		±2[a]	±3[a]	±3[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	±7[a]	
Telephone Visit			X		X		X		X	X					
Clinic Visit	X	X		X		X		X			X	X	X	X	X
Telephone Visit 4-point SMBG				X		X		X			X				
Lab Assessments															
Chemistry	X												X		X
Hematology	X												X		X
Pregnancy Screen[h]	X[h]														
ECG (local)	X														
HbA1c	X	X						X			X	X	X		X
Serum Samples for Biomarkers (Fasting)[i]		X[i]						X[i]					X[i]		X[i]
Anti-Glargine Antibody Titer		X		X				X			X		X		X
Fasting Serum Glucose[i]		X[i]											X[i]		X[i]
Other Transfer Data to eCRF (InForm™)															
Administer the ITSQ[i,k]		X[j]											X[j]		X[j,k]

Abbreviations: BG = blood glucose; DBP = diastolic blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; HbA1c = hemoglobin A_{1c}; HR = heart rate; ITSQ = Insulin Treatment Satisfaction Questionnaire; 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 when 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 postrandomization.

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

c Patients should perform two 7-point SMBG profiles during the 1-week period prior to these visits. The 7 points are: before the morning meal, midday meal, and evening meal; 2-hour postprandial measurements for the morning, midday meal, at bedtime and 3 am. In some instances (for example, between Visit 2 and Visit 3), some readings of the 7-point SMBG could overlap with those taken for the 4-point SMBG.

d Training should include instruction on glucose self-monitoring and the use of the glucose meter, record-keeping, hypoglycemia/marked hyperglycemia recognition and treatment, injection technique and device use, diet, and exercise. Additional training activity should be provided as needed throughout the study.

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

f Study sites will retain study diaries.

g Transfer values from the study diary if available.

h 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.

i The measurements should be done fasting before breakfast.

j Study sites will retain questionnaires.

k Administer this questionnaire only if the patient has received at least 1 dose of study medication.

Attachment 2. Protocol ABES Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
	Direct bilirubin
Platelets	Indirect bilirubin
Neutrophils, segmented	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Other	Albumin
Pregnancy Test[b]	
Hemoglobin A1c[a]	
Anti-glargine Antibodies[a]	**Fasting serum glucose**
Serum for nonpharmacogenetic biomarkers (C-peptide)	

Abbreviations: RBC = red blood cells; WBC = white blood cells.

[a] All laboratory tests to be performed at the 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 ABES 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-ABES Sampling Summary

Purpose	Sample Type	Estimated Amount per Sample	Number Samples	Estimated Total Amount
Screening tests[a]	Blood	3mL	2	6 mL
Standard laboratory test[a]	Blood	3 mL	7	21 mL
Immunogenicity samples	Blood	8 mL	5	40 mL
Nonpharmacogenetic biomarkers (C-peptide)	Blood	6 mL	3	18 mL
Total				85 mL
Hepatic Monitoring[b]	Blood	-	-	3 - 30

Abbreviation:

[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 ABES 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. ABES General Rules and Guidance for Intensive Insulin Therapy for ABES Study

1. Target glycemic goals would be the same for all patients (HbA1c <7%, preprandial capillary BGs: 79 to 126 mg/dL ([4.4 to 7.0 mmol/L], avoiding hypoglycemia).

2. Study treatment will start on the second day of randomization (Visit 2). At randomization, in the patients who were administered with basal-bolus therapies before enrollment with QD basal insulin and mealtime insulins will receive instruction to start new regimen with either QD LY2963016 or insulin glargine as basal insulin at the same doses next day. For those patients with BID prestudy basal as a part of basal-bolus regimen, the total daily prestudy basal insulin dose will be reduced by 20%, therefore, the study basal insulin dose will be 80% of the prestudy basal insulin dose. Insulin lispro will be administered with meals at the same doses as the patient's prestudy mealtime insulin dose while avoiding hypoglycemia, as determined by unit-to-unit conversion.

In the patients who were administered with premixed insulin will stick to prestudy regimen on the day of randomization, the total daily dosage at randomization will be the average for the sum of all insulin doses taken in the 3 days prior to randomization. The total daily dosage will then be split between basal and bolus insulin doses at the discretion of the investigator. For the treatment regimen, the initial basal insulin dose should be approximately 40% to 60% of the total daily dose. Then the initial bolus insulin dose (insulin lispro, 60% to 40% of the total daily dose) will be divided into 3 equal doses before 3 meals (or appropriate adjustment at investigator's discretion). The group of patients will be instructed by the investigators for receiving treatment with basal-bolus insulins in the trial.

The following examples are provided as a dose calculation tool of conversion from prestudy insulins to trial drugs.

Examples:

Patients will stick to pre-study insulin regimen at Visit 2, and new insulin regimen will start on the next day after visit 2.

a. Prestudy basal-bolus insulin regimen (QD basal + TID premeal) (1:1 conversion of basal-bolus insulin):

Lantus® 12U QD + Humulin R 6U (breakfast), 4U (lunch), 5U (dinner)

Will switch to:

LY2963016 (or Lantus®) 12U QD (same dosing time as previous) + Lispro 6U (breakfast), 4U (lunch), 5U (dinner)

b. Prestudy basal-bolus insulin regimen (BID basal + TID premeal) (1:1 conversion of bolus insulin and 80% of pre-study basal insulin):

NPH 10U (breakfast), 10U (dinner) + Lispro 6U (breakfast), 6U (lunch), 6U (dinner)

Will switch to:

LY2963016 (or Lantus®) (10U+10U)*80%=16U QD (daytime or evening/bedtime at the discretion of investigator) + Lispro 6U (breakfast), 6U (lunch), 6U (dinner).

c. Prestudy premixed insulin BID

In past 3 days, Humulin 70/30 18U (breakfast), 12U (dinner), total daily insulin dose: 30U

Will switch to:

LY2963016 (or Lantus®) 30U*40%=12U QD (daytime or evening/bedtime at the discretion of investigator) +6U for each meal (30U*60%=18U, equally divided into 3 meals), or appropriate adjustment at discretion of the investigators.

3. Insulin dose adjustments are mostly based upon SMBG levels. Four-point SMBG values will be reviewed during the telephone visit period and be recorded in the eCRF during the next investigator-site visit. In addition, 7-point SMBGs are also recorded during the 1-week period preceding office visits. The patient's SMBG results are to be used by the investigator to inform dose adjustments for a particular insulin dose (that is, adjustment based on glucose pattern or trends), as represented in Table A5.1.

Table A5.1. **Overview of Scenarios with Different Blood Glucose Levels and Corresponding Insulin-dose Adjustments***

Time	BG <80 mg/dL (<4.4 mmol/L)	BG >140 mg/dL (>7.8 mmol/L)
AM	Decrease Basal or Bedtime insulin	Increase Basal or Bedtime insulin
Pre-midday meal	Decrease AM lispro	Increase AM lispro
PM	Decrease Pre-midday meal lispro	Increase Pre-midday meal lispro
	Bedtime BG <100 mg/dL (<5.5 mmol/L)	Bedtime BG >160 mg /dL (>8.9 mmol/L)
BEDTIME	Decrease PM lispro	Increase PM lispro

Abbreviations: BG = blood glucose.

*   Adapted from Staged Diabetes Management.

Additional BG monitoring may be requested by the investigator while optimizing insulin doses. The investigator may adjust the insulin dose every 3 to 4 days (twice per week, [for example, via instructions to patient]) when appropriate, based on the patient's glycemic needs as reflected by SMBG measurements, and after the investigator has evaluated the role of diet and exercise on the resulting BG measurements.

4. All patients will have adjustments of basal insulin (LY2963016 or Lantus®) that are primarily investigator-driven during the phone and office visits, following Table A5.2. Based on the Study Schedule, these could occur every 7 days during the first 6 weeks, then every 2 to 6 weeks; but the investigator may also provide instructions to patients about increasing dose after 3 days or during the interval between visits until the dose is stable or the FBG goal has been achieved. To provide sufficient time for the HbA1c at Week 24 to be representative of a patient's glycemic control on their basal-bolus insulin regimen, most of the insulin titration should occur during the first 6 weeks of the Titration Period (Figure ABES.7.1.) or up to 12 weeks for patients who may need even more aggressive insulin intensification from their prestudy insulin regimen in order to achieve glycemic targets. During the Maintenance Period, it is expected that adjustments to insulin dose would be for safety such as hypoglycemia or unacceptable hyperglycemia.

Table A5.2. **Dose Adjustment for LY2963016 or Lantus®a**

FBG mg/dL	FBG mmol/L	Dose Change (Units)b
<50	<2.8	see belowc
50-90	2.8-5.0	see belowc
91-108	5.1-6.0	0
109-180	6.1-10	+2
181-270	10.1-15.0	+4
>270	>15.0	+6

Abbreviations: FBG = fasting blood glucose; TDID = total daily insulin dose.

a Fasting (morning) blood glucose values should be considered for adjusting the basal insulin.

b Based on most values during the last 1 to 2 weeks or the median of 3 most recent/applicable FBGs. In general, the change in TDID should not exceed more than 10 U per day or 10% of the current basal insulin dose, whichever is greater. If the dose adjustment needed is >10 U or 10% of basal insulin dose, the investigator should make a dosing decision based on the patient's highest BG level of the day.

c Based on most values during the 1 to 2 weeks or the median of 3 most recent/applicable FBGs. If glucose value is <5.0 mmol/L (<90 mg/dL) or the patient has symptoms consistent with hypoglycemia, the investigator will use their clinical judgment to decrease the insulin dosage appropriately.

5. Patients, in general, are to be instructed with their bolus insulin administration to achieve glycemic targets. Adjustments in the patients' bolus insulin intended to cover the meal are based upon a 2-day (corresponding premeal) pattern. Such adjustments to the bolus insulin intended to cover the meals are primarily investigator-driven and done during the office/phone visits in the course of the study (weekly for 6 weeks then every 2 to 6 weeks). In addition, the patients should also be encouraged to do daily SMBGs (before meals and at bedtime) and educated about/instructed on administering additional insulin if pre-meal BGs are above target at time of testing (that is, in addition to the dose intended to cover their meal). For patients who have relatively consistent carbohydrate intake from day to day, they may be provided with a pre-meal insulin algorithm described in 5a below. Patients who do carbohydrate counting alternatively may do pre-meal bolus calculation that includes insulin to cover the anticipated carbohydrate intake, and additional insulin if pre-meal BG happens to be above target, as described in 5b below.

The investigator could also consider keeping close to the 50:50 general guidance regarding basal mealtime insulin distribution in adjusting the insulin doses. However, it should be noted that this ratio may vary and the initial basal insulin dose is recommended to be approximately 40% to 60% of the total daily dose.

When BG is not determined before a meal, then the mealtime insulin dose administered would be the dose as if the BG were at target (79 to 126 mg/dL). Patients should be encouraged to regularly check pre-meal SMBG levels to optimize glycemic control.

5a. Adjustment of insulin doses for patients not using carbohydrate counting:

At Visit 2 (randomization), patients with basal-bolus regimen are switched to insulin lispro at each meal using a unit-to-unit conversion from prestudy mealtime bolus insulin doses. For those patients with premixed insulins before the study, the initial bolus insulin dose (insulin lispro) is recommended to be approximately 60% to 40% of the total prestudy insulin dose and will be divided into 3 equal doses before 3 meals or appropriate adjustment at investigator's discretion. For patients who have relatively constant carbohydrate per meal, each mealtime dose will have to be adjusted based on a 3-day glucose pattern for corresponding meals (for example, for the morning meal insulin dose, the midday meal glucose levels from 3 days, preferably the 3 most recent days, or from the available 4- or 7-point SMBGs, if applicable) according to Table A5.3.

Table A5.3.   Mealtime Insulin Lispro Adjustments to Cover Patients Not Carbohydrate Counting[a]

BG mg/dL based on 3-day pattern for corresponding meal	BG mmol/L	Dose Change (Units)[b]
< 50 (<80 mg/dL at bedtime)	<2.8 (<4.4 at bed time)	-3 to -4
50-80 (80-100 mg/dL at bedtime)	2.8-4.4 (4.4-5.5 at bed time)	-1 to -2
81-140 (101-160 at bedtime)	4.5-7.8 (5.6-8.8 at bed time)	0
141-180 (161-200 at bedtime)	7.9-10.0 (8.9-11.1 at bed time)	+1 to +2
>180 (>200 at bedtime)	>10.0 (11.1 at bed time)	+2 to +4

Abbreviations: BG = blood glucose

[a] Adapted from Staged Diabetes Management. Pre-midday meal BG values in the past 3 to 14 days are considered for dose adjustment of insulin lispro at the morning meal, pre-evening meal BG values for dose adjustment of insulin lispro at midday meal, and bedtime BG for dose adjustment of insulin lispro given at the evening meal. Note that the target BG for bedtime is between 100 and 160 mg/dL (5.5 and 8.9 mmol/L).

[b] Based on glucose pattern from BG readings on 3 separate days from previous 1 to 2 weeks (preferably most recent readings).

The insulin adjustments in Table A5.3address the mealtime insulin dose intended to cover the patient's carbohydrate intake during the meal (presumed consistent from day to day), and are primarily investigator-driven based on patient's previous glucose trends as described above. A mealtime insulin dose directed to cover a meal could only bring a patient's BG level back to target if the patient started off with BG levels that are right on target. If the patient's pre-meal BG level is elevated at time of testing, additional insulin should also be given to bring the BG level closer to target using a "correction bolus," which allows the patient to bring down high blood glucose levels closer to their target blood glucose level after the meal. The investigator may determine the appropriate "correction bolus" for the patient to administer when pre-meal BG levels are above target, based on clinical judgment, taking into account the patient's performance with previous/current insulin regimen and recent glucose profiles, and appropriate patient education should be provided when needed. Alternatively, the correction bolus may initially be calculated as follows:

Correction Bolus = 1800/TDID = estimated drop in BG (mg/dL) level per unit of Humalog® administered.

Fine-tuning the patient's correction bolus may be done based on the investigator's clinical assessment and guided by the patient's SMBG results or clinical presentation. While the patient

may keep in mind this correction bolus and use it to calculate their insulin lispro dose before each meal, a mealtime insulin algorithm may also be offered to patients to incorporate the correction bolus with the mealtime insulin dose intended to cover the meal as illustrated in example below.

Example 1: Patient with prestudy insulin regimen consisting of 20 U Lantus® and insulin lispro given as 4 U at the morning meal, 6 U at the midday meal, and 6 U at the evening meal (and, thus, started on similar regimen at randomization) would have:

correction bolus = 1800/ TDID = 1800/36 = 50

(that is, each unit of insulin could decrease BG level by approximately 50 mg/dL).

If the patient reports that their individualized glucose targets are between 70 and 140 mg/dL (for example, a tendency to develop hypoglycemia occurs if patient administers additional "correction" insulin if BG is <140 mg/dL), a mealtime insulin algorithm could be constructed from the information below, using the correction bolus as the increment between the upper limit of the range from one BG range to the next (for example, 140 + 50 = 190, 190 + 50 = 240, etc.). (NOTE: If a patient has not been experiencing hypoglycemia or does not appear to be too sensitive to insulin, one could use 79 to 126 mg/dL as the range at which no correction dose is applied.) Each day then, the patient would administer the doses indicated for respective meals based on results of SMBG values at mealtime.

If the premeal BG is:	The pre-morning meal dose of insulin lispro is:	The pre-midday meal dose of insulin lispro is:	The pre-evening meal dose of insulin lispro is:
<70 mg/dL	3	5	5
70-140 mg/dL	4	6	6
141-190 mg/dL	5	7	7
191-240 mg/dL	6	8	8
>240 mg/dL	7	9	9

Note also that a patient's insulin doses that are intended to cover meals (derived from prestudy doses) are plugged in the "base case," where pre-meal BG is assumed to be at target as a start (for example, 70 to 140 mg/dL in the example above). If a patient has elevated HbA1c, then it could be expected that the patient will likely have to increase "base case" dose. An example is provided below to illustrate how this mealtime insulin algorithm is refined during follow up, when the pre-meal insulin doses at "base case" need to be adjusted.

Example 2: Upon follow up of the patient in the example above, it was noted that there was a consistent elevation in bedtime values averaging approximately 260 mg/dL. (Thus, the patient has been administering an extra 2 U of insulin every bedtime to correct this high reading.) Guided by Table A5.3, the investigator instructs the patient to increase the pre-evening meal dose by 3 U (thus, 6 + 3 = 9 U to be administered at the evening meal when BG are within target). Adjustments to the mealtime insulin algorithm, considering the same correction bolus calculated earlier, will result in refinements below (**changes bolded**):

If the premeal BG is:	The pre-morning meal dose of insulin lispro is:	The pre-midday meal dose of insulin lispro is:	The pre-evening meal dose of insulin lispro is:
<70 mg/dL	3	5	5
70-140 mg/dL	4	6	**9**
141-190 mg/dL	5	7	**10**
191-240 mg/dL	6	8	**11**
>240 mg/dL	7	9	**12**

(In the next few days, if the adjustments reflected above are effective and sufficient, then the patient's bedtime BG levels would be expected to fall within or closer to target such that patient does not need to give any extra insulin at bedtime as the hyperglycemic episodes have been averted by the increased pre-evening meal insulin dose.)

5b. Adjustment of mealtime insulin doses of patients doing carbohydrate counting.

For patients who practice carbohydrate counting, the patient's pre-meal insulin dose administered is based on the amount of carbohydrate they are about to consume with the meal (for example, 0.5 to 2.0 units of insulin /10 to 15 g carbohydrate [that is, per fruit exchange]) and a correction bolus (similar calculation as 5a) if their pre-meal PG is above target.

6. The investigator may provide guidance on bolus insulin adjustments, based on the projected exercise pattern and level of stress during the period of insulin action, when applicable. Anticipated exercise adjustment: 50% reduction in insulin dose with anticipated exercise. Adjustment when under increased stress is approximately a 10% increase in dose.

Attachment 6. Protocol ABES World Health Organization (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 hyperglycemia, but to prevent spontaneous ketosis and death.

Type 2 Diabetes Mellitus: Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, 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 hyperglycemia 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 7. Protocol Amendment I4L-GH-ABES(a) Summary: A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog, LY2963016, to Lantus® in Combination with Mealtime Insulin Lispro in Adult Chinese Patients with Type 1 Diabetes Mellitus

Overview

Protocol I4L-GH-ABES 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 date and last patient visit date in synopsis were updated.

- For acarbose usage, 1) inclusion criteria was expanded to include patients with previous treatment of acarbose only as oral antihyperglycemic medication; 2) it was added as a stratification factor, and 3) discontinuation of acarbose at randomization was added in exclusion criterion [17], Section 8.2.

- 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.

- Sentence related to patients' self-titration of mealtime insulin dose based on SMBG readings in Section 9.4 was modified to clarify that insulin dose titration will be driven by the investigator.

- Tests of fasting serum glucose at Visit 2, Visit 13, 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 randomization to 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).

LY2960316

- Added an abbreviation of SD (standard deviation) in Section 4.

- In Attachment 3, estimated sampling for standard laboratory test was updated, and total amount was changed accordingly.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~.
	Additions have been identified by the use of <u>underscore</u>.

2.   Synopsis

Length of Study:
Estimated first patient visit: Mar 201~~7~~<u>8</u>   Estimated last patient visit: Sep 201~~9~~<u>20</u>

Statistical Methods:

<u>Sample Size:</u>

Based on the primary objective, to show noninferiority of LY2963016 to Lantus® at the 0.40% noninferiority margin (NIM), 109 completers per arm (218 total) are needed at 24 weeks. This calculation assumes no treatment difference in HbA1c between LY2963016 and Lantus®, a common <u>standard deviation (SD)</u> of 1.05% for change from baseline in HbA1c, a two-sided significance level of 0.05, and over 80% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients is 129 per arm (258 total).

Blinded sample-size reestimation may be performed when approximately 40% of the subjects have been enrolled in the study and finished 24-week of treatment, or about 6 months prior to the completion of enrollment, depending on which occur first by team assessment.

<u>Statistical</u>:

The primary efficacy outcome is 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®), stratification factors screening HbA1c Stratum, prestudy treatment, and prestudy metformin <u>or acarbose</u> usage (~~yes or no~~<u>metformin only, acarbose only, or neither</u>), 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 with the same MMRM model on per-protocol (PP) population and with an analysis of covariance (ANCOVA) model on FAS population.

4.   Abbreviations and Definitions

<u>**SD**</u>   standard deviation

<u>**TEAE**</u> ~~(treatment-emergent adverse event)~~   ~~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.~~ <u>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>

7.1.   Summary of Study Design

Patients will come to the investigator site for Visits 2, 4, 6, 8, 11, 12, ~~and~~ 13<u>, and 801</u> for various study assessments during the treatment period. Patients will be contacted over the telephone for Visits 3, 5, 7, 9, <u>and 10</u>~~, and 801~~ (described as "Telephone Visits" in Section 7.2.2.2) to assess their response to study drug (including 4-point SMBG, AEs, and hypoglycemia) and/or to further

adjust insulin doses, if needed. Insulin dose adjustments will be done in both treatment arms to help patients achieve glycemic targets (HbA1c <7%, preprandial capillary BGs 79 to 126 mg/dL [4.4 to 7.0 mmol/L]) while minimizing/avoiding hypoglycemia. Patients will come for a clinic visit at Visit 13 for their final assessments at the completion of 24 weeks. At approximately 4-weeks post-treatment endpoint, patients will have a final ~~telephone~~clinic visit (Visit 801), at which information will be collected according to the Study Schedule (Attachment 1).

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 ABES.7.1 illustrates the study design.
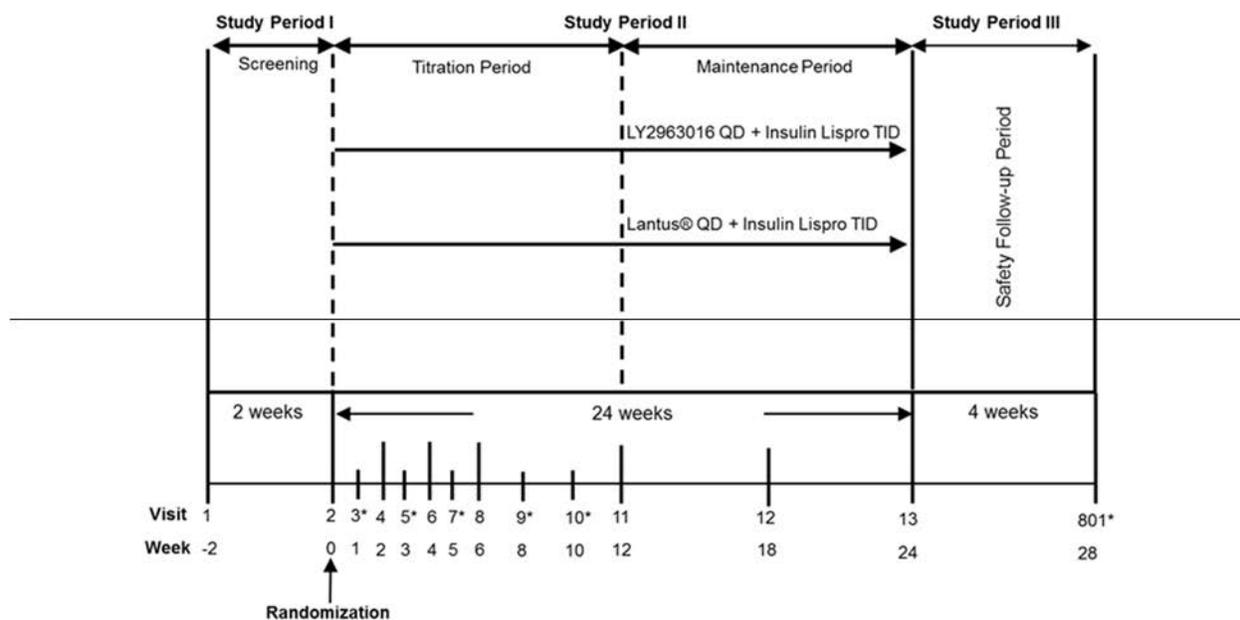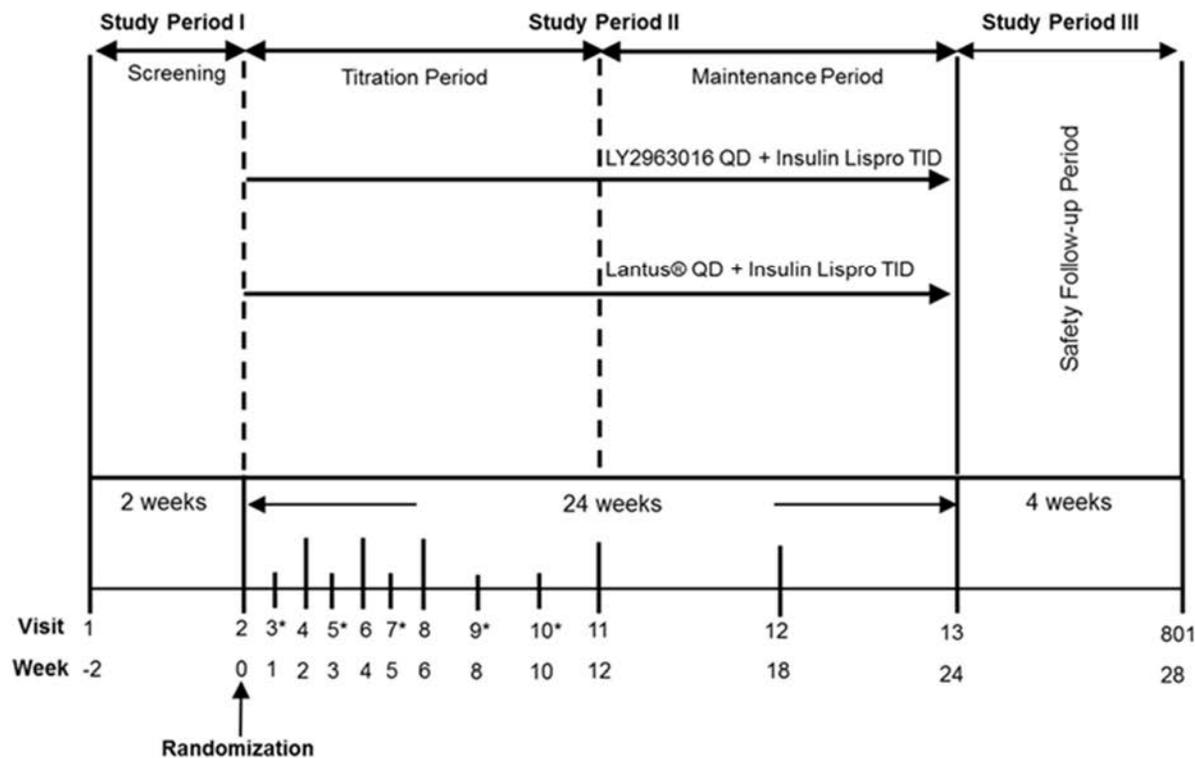
7.2.2.2.1. Patients Eligible for Randomization at Visit 2

- Eligible patients will be randomized to 1 of 2 treatment groups by a random assignment based on Visit 1 HbA1c, prestudy treatment with basal-bolus insulin or premixed insulin, and prestudy ~~treatment with metformin or not~~ metformin or acarbose usage (metformin only, acarbose only, or neither). For patients with prestudy treatment of metformin or acarbose (excluding those taken both) prior to Visit 1, their concomitant OAM will be discontinued at Visit 2.

7.2.2.3. Telephone Visit 1

Between each investigator-site visit, patients will have a telephone visit with the investigator or designee at Visit 3, 5, 7, 9, and 10~~, and 801~~.

7.2.2.4. Study Visits (Visit 3 to Visit 13 or Early Discontinuation)

Patients will come to the investigator site at 2-week intervals between Visit 2 and Visit 8. From Visit 8 to Visit 13, patients will come to the clinic at 6-week intervals. Visit 801 is a 4-week follow-up ~~telephone~~clinic visit (Attachment 1).

7.2.2.5. 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). Patients who discontinue early from the study will undergo all

end-of-study procedures <u>and complete Visit 801</u> as outlined in Attachment 1. These data will be collected and stored for future reference/analyses, if needed.

7.2.3.   Blood Glucose Monitoring Plan

- Patients will be instructed to complete 2 separate 7-point SMBG profiles in the 1-week period prior to each office visit <u>from Visit 2 to Visit 13</u> (or at ED) (preferably most recent readings). <u>At Visit 801, only 4-point SMBG is required to be collected.</u> The SMBG profiles will consist of:

  - before the morning meal, midday meal, and evening meal; 2-hour postprandial measurements for the morning, midday meal, at bedtime and 3 am.

Throughout the study, patients will be expected to routinely check their fasting, premeal, and bedtime BG values daily to help assess the need for dose adjustments and to guide dosing of the mealtime/fast-acting insulin lispro (Attachment 5). Patients may be requested by investigators (as they deem necessary) to perform more intensive self-monitoring, if clinically indicated. Both 4-point and 7-point SMBG values will be recorded in the diaries and transcribed into the eCRF at the office visit ~~and at Visit 801~~ (Attachment 1 and Attachment 5).

8.2.   Exclusion Criteria

[17] Have taken any oral antihyperglycemic medications (OAMs) within 3 months prior to Visit 1. Except for those patients with metformin <u>or acarbose</u> at a stable dose for more than 90 days prior to Visit 1 <u>(excluding those taken both)</u>, ~~they~~<u>their concomitant OAM</u> will <u>be</u> discontinue<u>d</u> ~~metformin~~ at randomization before the study treatment.

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 by stratified randomization to 1 of the 2 treatment arms, in a ratio of 1:1, via random assignment using the interactive web response system. To achieve between-treatment group comparability, patients will be stratified by screening HbA1c stratum (<8.5%, ≥8.5%), pre-study treatment (Lantus®-bolus, other basal-bolus, premixed insulin), and pre-study metformin ~~usage (yes or no)~~ <u>or acarbose usage (metformin only, acarbose only, or neither)</u>.

9.4.   Rationale for Selection of Doses in the Study

At randomization, in the patients who were administered with basal-bolus therapies before enrollment, QD LY2963016 will be started at the same doses as the QD prestudy basal insulin. For those patients with BID prestudy basal insulin as part of basal bolus regimen, the total daily prestudy insulin dose will be reduced by 20% at randomization to LY2963016 or insulin glargine, therefore, the study basal insulin dose will be 80% of the prestudy basal insulin dose. Insulin lispro will be administered with meals at the same doses as the patient's prestudy mealtime insulin dose while avoiding hypoglycemia, as determined by unit-to-unit conversion. Based on the patient's prestudy mealtime insulin regimen relative to his/her lifestyle, the investigator could

translate the patient's previous mealtime insulin regimen so that the patient's prestudy mealtime insulin is replaced with a similar dose of insulin lispro to be used during the study. During the course of the study, the patient's mealtime insulin does will be adjusted and optimized by investigators. During the course of the study, the patient's mealtime insulin doses will be adjusted and optimized by the investigator. ~~as he or she is encouraged to do SMBG readings before meals and instructed to titrate his or her mealtime insulin dose as guided by those premeal readings, in addition to investigator - directed insulin dose adjustments guided by the previous days' glucose patterns.~~ Study participants will administer mealtime insulin doses before meals to provide insulin coverage for the meal, as well as a correction dose if the premeal BG reading is above target.

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 caucation, 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.

10.4.2.1. 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).

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

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), 109 completers per arm (218 total) are needed at 24 weeks. This calculation assumes no treatment difference in HbA1c between LY2963016 and Lantus®, a common standard deviation (SD) of 1.05% for change from baseline in HbA1c, a two-sided significance level of 0.05, and over 80% power. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients is 129 per arm (258 total).

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.

12.2.6. 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 postbaseline visit in HbA1c level as the dependent variable with treatment (LY2963016, Lantus®), pre-study treatment (Lantus®-bolus, other basal-bolus, premixed insulin), and pre-study metformin ~~usage (yes or no)~~ or acarbose usage (metformin only, acarbose only, or 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.

A second secondary analysis of the primary efficacy outcome will use an ANCOVA model with FAS population. The ANCOVA model will include treatment, pre-study treatment, and pre-study metformin or ~~usage (yes or no)~~ or acarbose usage (metformin only, acarbose only, or 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 postbaseline 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.

12.2.9.2. 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.

12.2.9.3. Hypoglycemic Events

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, prestudy treatment, and prestudy metformin or acarbose usage. 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.

12.2.9.4. Laboratory Measures

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, prestudy treatment, and prestudy metformin or acarbose usage 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.

12.2.10. Subgroup Analyses

- Prestudy metformin or acarbose use: (metformin only, acarbose only or neither)

The change in HbA1c from baseline to 24-week endpoint will be analyzed using MMRM with treatment, visit, prestudy treatment, prestudy metformin or acarbose usage, 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.

Attachment 1.   Protocol ABES Study Schedule

Description of Event							Visit								
	1	**2**	**3***	**4**	**5***	**6**	**7***	**8**	**9***	**10***	**11**	**12**	**13**	**801***	**ED#**
Week of Study	-2	0	1	2	3	4	5	6	8	10	12	18	24	28	
Allowable Deviation (Days)a	±7a		±2a	±3a	±3a	±7a	±7a	±7a	±7a	±7a	±7a	±7a	±7a	±7a	
Telephone Visit			X		X		X		X	X				~~X~~	
Clinic Visit	X	X		X		X		X			X	X	X	<u>X</u>	X
Clinic Assessments															
Concom. Meds[b,i]	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X[b]	X	X	X	X[i]	X
Adverse Events[b,i]	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X[b]	X	X	X	X[i]	X
Hypoglycemic Episodes[b,i]		X	X[b]	X	X[b]	X	X[b]	X	X[b]	X[b]	X	X	X	X[i]	X
4-point SMBG[b,i]			X[b]		X[b]		X[b]		X[b]	X[b]				X[i]	
Study Drug/Device/Training and Education[d]															
Distribute Study Diary	X	X		X		X		X			X	X	X		<u>X</u>
Transfer Diary Data to eCRF (InForm™)															
Insulin Therapy Dose (day prior to visit)[i]		X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X
Telephone Visit 4-point SMBG[i]			X		X		X			X	X			~~X~~[i]	
Lab Assessments															
Serum Samples for Biomarkers (Fasting)[i]		X[i]						X[i]					X[i]		<u>X</u>[i]
Anti-gGlargine aAntibody tTiter		X		X				X			X		X		X
Fasting Serum Glucose[i]		<u>X</u>[i]											<u>X</u>[i]		<u>X</u>[i]

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

^b Adverse events, hypoglycemic episodes, concomitant medications, and the last three available 4-point SMBG profiles 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, evening meals, and at bedtime.

ⁱ ~~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 ABES Clinical Laboratory Tests**

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
	Direct bilirubin
Platelets	Indirect bilirubin
Neutrophils, segmented	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Other	<u>Albumin</u>
Pregnancy Test[b]	
Hemoglobin A1c[a]	~~Albumin~~
Anti-glargine Antibodies[a]	**<u>Fasting serum glucose</u>**
Serum for nonpharmacogenetic biomarkers (C-peptide)	-

Attachment 3. **Protocol ABES Estimated Sampling Summary**

Purpose	Sample Type	Estimated Amount per Sample	Number Samples	Estimated Total Amount
Screening tests[a]	Blood	3mL	2	6 mL
Standard laboratory test[a]	Blood	3 mL	~~6~~7	~~18~~21 mL
Immunogenicity samples	Blood	8 mL	5	40 mL
Nonpharmacogenetic biomarkers (C-peptide)	Blood	6 mL	3	18 mL
Total				8~~2~~5 mL
Hepatic Monitoring[b]	Blood	-	-	3 - 30

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