Statistical Analysis Plan

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Title:	An open-label, randomized, multicenter, phase III study to compare the immunogenicity, efficacy, and safety of Gan & Lee Pharmaceuticals Insulin Glargine Injection to Lantus® (insulin glargine injection) in adult subjects with Type 2 diabetes mellitus
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Approvals

Sponsor

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Table of Contents

1. Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Gan & Lee Pharmaceuticals, USA Corporation Protocol GL-GLAT2-3002.

2. Scope

The initial version of the SAP drafted within three months of the finalization of the case report forms (CRF), will require sign off from the Project Manager, Biostatistician, and the sponsor and includes the following outline:

- Study objectives
- Study design
- Endpoints analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, immunogenicity analysis, concomitant medications, adverse events (AEs), laboratory data and physical examinations

3. Introduction

This SAP should be read in conjunction with the study protocol and case report forms (CRF). This version of the plan has been developed using the protocol amendment 3 dated 25APR2019 and CRF dated 15-Apr-2019. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The study is an open-label study, investigators and subjects are not blinded. However, to avoid the introduction of operational bias into final study results and to increase the interpretability and reliability of the data, certain roles of the Sponsor and study team will be blinded. Details will be provided in the Data Blinding and Documentation of Aggregate Data Dissemination Plan. A final version of the SAP will be issued for sponsor approval prior to database lock, at which point the blinded team members will become unblinded to the actual randomization codes in aggregate form.

3.1 Changes from Protocol

Per FDA comment, Wald method has been replaced with logistic regression approach to calculate the difference in proportions along with the corresponding 90% CI for the primary endpoint and corresponding sensitivity analyses. The delta method will be used to calculate the standard error for the difference and the associated confidence interval.

Also, per FDA suggestion, separately in each treatment group, the imputation will use outcomes in patients who discontinued treatment but provided a visit Week 26 glycosylated hemoglobin (HbA1c) measurement if sufficient data are available to impute outcomes in patients without actual visit Week 26 recorded results, under the assumption of missing not at random (MNAR). Full details are provided in Section 11.7 below.

4. Study Objectives

4.1 Primary Study Objective

- To evaluate equivalence of Gan & Lee Insulin Glargine Injection and Lantus® in terms of immunogenicity by comparing the proportions of subjects between the two treatment arms who develop treatment induced anti-insulin antibodies (AIAs), which is defined as either treatment emergent AIA development or important increase (at least 4-fold) in AIA titers up to visit Week 26.

4.2 Secondary Study Objectives

4.2.1 Immunogenicity

- To evaluate the percentage of subjects with negative anti-insulin antibodies (AIAs) at baseline who develop confirmed positive AIA up to visit Week 26, the percentage of subjects with at least a 4-fold increase in titers compared to baseline value, mean change from baseline in AIA titers between treatment groups, the percentage of subjects with confirmed positive AIA who develop any anti-insulin neutralizing antibodies up to visit Week 26, and percentage of subjects who develop confirmed positive AIA up to visit Week 26 of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus®

4.2.2 Safety

- To evaluate the safety of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus®

4.2.3 Efficacy

- To evaluate the efficacy of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus® by comparing subjects' average change from baseline of HbA1c at visit Week 26 between the two treatment arms. This secondary efficacy objective is not specified in the protocol objectives as a key secondary objective, however it is specified as a key secondary endpoint, and the evaluation of the efficacy measured by change from baseline of HbA1c at visit Week 26 of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus® will undergo statistical analysis as a key secondary endpoint of the study.
- To evaluate the percentage of subjects who achieve a fasting blood glucose (FBG) test result of ≤ 8.0 mmol/L (≤ 144.0 mg/dL) at visit Week 26, the percentage of subjects who achieve a HbA1c of < 7.0% at visit Week 26 of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus®

4.3 Exploratory Objective

- To investigate the retrospective hypoglycemic rate and time in hypoglycemia and hyperglycemia using continuous glucose monitoring (CGM) data

5. Study Design

This open-label, randomized, multicenter study is designed to compare the immunogenicity, efficacy, and safety of Gan & Lee Insulin Glargine Injection compared with that of Lantus® in subjects with Type 2 diabetes mellitus to determine equivalence.

Subjects between the ages of 18 and 75 who meet the study inclusion criteria and none of the exclusion criteria as defined in the protocol, will be centrally randomly assigned in a 1:1 allocation ratio to receive either Gan & Lee Insulin Glargine Injection or Lantus®. Randomization and the level of blinding in this study are further described in Section 5.2. Subjects will participate for 2 weeks' screening + 26 week treatment + 4 week following up in total a maximum of 32 weeks in the study. Recruitment will stop when approximately 275 subjects have been randomly assigned to each treatment group. The study will end when the last subject completes the end-of-study visit, or discontinues the study treatment, whichever occurs first.

During the 2 weeks between screening and randomization, once subjects already on basal insulin are determined eligible for the study, they will have their insulin dosing optimized according to Table 1. They will also have any appropriate adjustments in their other antidiabetes medication (OAM) dosing that may

be required because of the optimization of their insulin dosing. Subjects who are insulin-naïve will have their OAM dosing optimized to prepare them for starting basal insulin therapy.

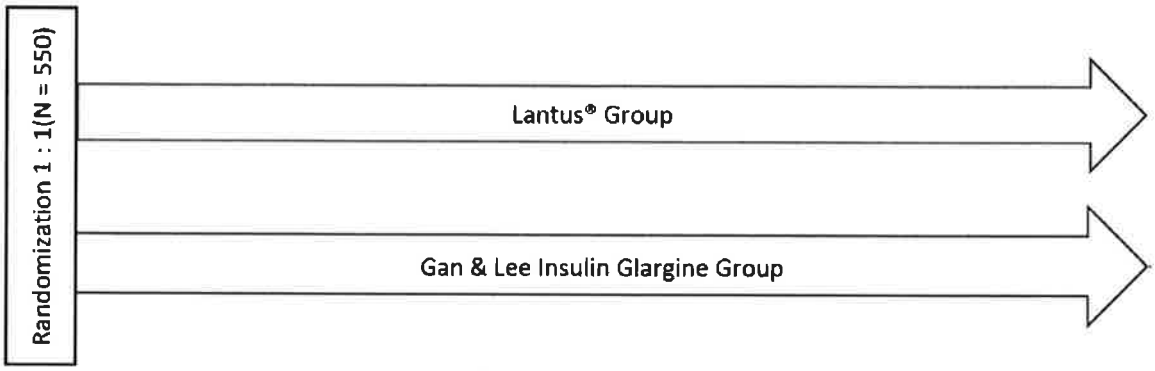
Table 1: Basal Insulin Dose Adjustment Based on Fasting Glucose Result between Screening and Randomization

Lowest Average Fasting Plasma Glucose (Pre-Breakfast) Value for 3 Days	Adjust Basal Insulin Dose (Units per Dose)
> 271 mg/dL (> 15.1 mmol/L)	+ 6 U
181 – 270 mg/dL (> 10.1 – 15.0 mmol/L)	+ 4 U
151 – 180 mg/dL (> 8.4 – 10.0 mmol/L)	+ 2 U
131 – 150 mg/dL (> 7.3 – 8.3 mmol/L)	+ 1 U
71 – 130 mg/dL (> 3.9 – 7.2 mmol/L) (Target Level)	Maintain Current Dose
56 – 70 mg/dL (3.1 – 3.9 mmol/L)	- 2 U
< 56 mg/dL (< 3.1 mmol/L)	- 4 U

At the screening visit, the subject will have an Abbott FreeStyle Libre Pro Flash Glucose Monitoring sensor applied to the back of the upper arm to record the interstitial glucose concentration every 15 minutes for 8 days. At the randomization visit (Visit 2), subjects will receive supply of insulin pens with Investigational Product (IP) and the Investigator or designee will train subjects on all study procedures and proper dose administration.

Subjects in both treatment groups will be assessed every 2 weeks after Visit 2 (randomization visit) through Week 22 (these assessments will be done either through in person clinical visit or will be done through a telephone call) and then at Week 26; they will attend 9 clinic visits (the screening visit, the randomization visit (Day 1, see Section 7.1), and at Weeks 2, 4, 8, 12, 16, 20, and 26), 2 brief visits with no study assessments during which a CGM sensor will be applied (8-10 days before the visits at Weeks 12 and 26 for subjects to wear for a 8-day period), and they will be contacted by telephone at Weeks 6, 10, 14, 18, and 22. The Week 26 visit (Visit 9) will be the end-of-treatment (EOT) visit (see Section 7.1). See Figure 1 for summary of study visits. All study procedures and assessments (see Table 2) are described in more detail in Section 8.1 in the study protocol.

Figure 1: Study Diagram



V1	V2	V3	V4	TC	V5	TC	—	V6	TC	V7	TC	V8	TC	—	V9 EOT/ ET	FU TC
d -14 to d-1	d1	W2 ±3d	W4 ±3d	W6± 3d	W8 ±3d	W10 ±3d	W11	W12 ±3d	W14 ±3d	W16 ±3D	W18 ±3D	W20 ±3D	W22 ±3D	W25	W26 ±3d	30 d after V9

d = day; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; TC = telephone call; V = visit; W = week

Note: At weeks 11 and 25, subjects will attend a brief visit for application of a continuous glucose-monitoring sensor.

Table 2: Study Procedures and Assessments

Visit	1	2	3	4	TC	5	TC	---	6	TC	7	TC	8	TC	---	9[a]	FU TC
Day or Week	Day -14 thru Day -1	Day 1	Week 2 ±3d	Week 4 ±3d	Week 6 ±3d	Week 8 ±3d	Week 10 ±3d	Week 11	Week 12 ±3d	Week 14 ±3d	Week 16 ±3d	Week 18 ±3d	Week 20 ±3d	Week 22 ±3d	Week 25	Week 26 ±3d	30 d ±3d after Visit 9
Informed Consent	X																
Eligibility	X																
Medical History	X																
Randomization		X															
Concomitant Medications[b]	X	X	X	X	X	X	X		X	X	X	X	X	X		X	
Adverse Events	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X[j]
Vital Signs	X	X	X	X		X			X		X		X			X	
Height, Body Weight, BMI[c]	X	X	X	X		X			X		X		X			X	
Hematology & Chemistry[d]	X								X							X	
Fasting Blood Glucose	X	X	X	X		X			X		X		X			X	
HbA1c	X					X					X					X	
Pre-dose Blood Sample for AIA	X								X							X	
UA, Pregnancy Test[e]	X	X	X	X		X			X		X		X			X	
12-Lead ECG	X															X	
Physical Examination	X															X	
Glucometer and Supplies Issued, and Training	X																
Apply CGM Sensor and Issue Mealtime & Insulin Dose Record[f]	X							X							X		
Collect CGM Sensor and Review Mealtime & Insulin Dose Record		X							X							X	
IP and Other Supplies Issued[g]		X	X	X		X			X		X		X				
Subject Training on IP[h]		X															
Review Insulin & OAM Use, Glucose Results, & Hypoglycemic Events Record[i]		X	X	X	X	X	X		X	X	X	X	X	X		X	
Collect Used Insulin Kits			X	X		X			X		X		X			X	

AIA = anti-insulin antibody; BMI = body mass index; CGM = continuous glucose monitoring; d = Day; ECG = electrocardiogram; HbA1c = glycosylated hemoglobin; IP = investigational product; OAM = other anti-diabetes medication; TC = telephone call; UA - urinalysis

[a] Any subject who withdraws from the study before Week 26 will have the Visit 9 procedures performed for their end-of-study visit.
[b] At screening, prior and concomitant medications will be collected. At every visit (except for visits to apply a CGM sensor) or telephone call, the Investigator or designee will inquire about concomitant medications, including insulin products taken before the first dose of IP.
[c] Height and body weight will be measured at the screening visit, and at subsequent visits, only body weight will be measured. The BMI will be calculated and recorded whenever the body weight is measured.
[d] Routine laboratory testing will include a complete blood count, a metabolic chemistry panel with serum lipids, a thyroid stimulating hormone and free thyroxine.
[e] Women of childbearing potential will have a urine pregnancy test at screening and at each clinic visit.
[f] At the screening visit and at Weeks 11 and 25, subjects will attend a brief visit to have a CGM sensor applied. This visit should take place between 8 and 10 days before the scheduled visits at Weeks 12 and 26, respectively. Subjects will also be given a Mealtime & Insulin Dose Record to be completed during the 8-day CGM period that they will bring to the next visit.
[g] At these visits, subjects will be issued a supply of IP sufficient to last until the next clinic visit. They can also obtain more supplies for glucometer testing if needed.
[h] At Visit 2, the Investigator or designee will instruct the subject on all study procedures including proper IP administration.
[i] Subjects will bring the Hypoglycemic Events Record to each visit for review.
[j] Only serious adverse events to be queried.

Note: See Section 5 and Table 1 for details about insulin and OAM dose optimization.

5.1 Sample Size and Power

Enrollment was planned for 550 subjects overall (275 subjects per treatment group). The primary analysis for immunogenicity primary endpoint was to be an equivalence test for the difference in proportion of subjects who develop treatment-induced AIAs between Gan & Lee insulin Glargine Injection and Lantus® using the 2 Wald one-sided tests (TOST) approach with α=0.05 (Chow and Shao 2002 (1)). After scientific and regulatory review, the method to evaluate immunogenicity equivalence will be the 90% confidence intervals of risk difference from logistic regression analysis (see Section 3.1). Under this newly adopted approach, no power loss is expected.

This sample size of 275 subjects per treatment group was chosen to achieve over 80% power using the TOST equivalence test for two proportions, a risk difference of zero and equivalence margins dependent on the observed treatment-induced AIA rate per Table 3 below. For example, a sample size of 550 will provide approximately 85% power for the TOST equivalence test using a treatment-induced AIA rate of 30% and a margin of 12% (See Table 3).The treatment-induced AIA is defined as newly confirmed positive AIA development or important (at least a 4-fold) increase in AIA titers, after baseline and up to visit Week 26 (see the definition of Primary Endpoint in Section 6.1 and Section 7.2). No drop outs are considered in the calculation. A larger than expected early discontinuation rate was observed as part of study monitoring activities and therefore protocol amendment 3 approved on 25-Apr-2019 included procedures to encourage subjects to return for assessments even if they have discontinued treatment early.

The appropriate similarity margin, based on the actual observed event rate for the intended reference product, will be used for final analysis after database lock as summarized in the Table 3 below. The power calculation in the table was adapted for a sample size of 550 using the treatment-induced AIA rate for the reference product. Linear interpolation will be used for values between AIA rates in the table.

Table 3: Similarity margins for actual observed event rate of proposed biosimilar to insulin glargine for various immunogenicity event rates

Treatment-induced AIA Rate for the Reference Product	Margin	Power
10%	7.9%	83%
15%	9.3%	83%
20%	10.5%	84%
25%	11.3%	84%
30%	12.0%	85%
35%	12.5%	85%
40%	12.8%	85%
45%	13.0%	85%
50%	13.1%	85%
55%	13.0%	85%
60%	12.8%	85%
65%	12.5%	85%
70%	12.0%	85%
75%	11.3%	84%
80%	10.5%	84%
85%	9.3%	83%
90%	7.9%	83%

Sample size calculations were performed using EAST Version 6.4 (East 6 (2020) (2)).

5.2 Randomization

Subjects will be randomly assigned in a 1:1 ratio to Gan & Lee Insulin Glargine Injection or Lantus® treatment. Subject randomization will use a randomly permuted block design with varying block sizes and without stratification.

Registration and randomization will take place using a centralized Interactive Web Response System (IXRS). At registration, the IXRS will assign a unique subject identification number that will be used on all of that subject's eCRFs and serious adverse event (SAE) report forms.

This is an open-label study, however, to avoid the introduction of operational bias into final study results and to increase the interpretability and reliability of the data, certain roles of the Sponsor and study team will be blinded. Details are provided in the Data Blinding and Documentation of Aggregate Data Dissemination Plan (hereafter referred to as the Blinding Plan).

6. Endpoints and Covariates

6.1 Primary Endpoint

6.1.1 Immunogenicity

- The percentage of subjects in each treatment group who develop treatment-induced AIAs, defined as either newly confirmed positive AIA development or important increase (at least a 4-fold) in AIA titers after baseline and up to visit Week 26 (refer to Section 7.2 for detailed definition).

6.2 Key Secondary Endpoint

6.2.1 Efficacy

- The change in HbA1c from baseline at visit Week 26

6.3 Other Secondary Endpoints

6.3.1 Immunogenicity

- The percentage of subjects in each treatment group with negative AIA at baseline who develop confirmed positive AIA after baseline and up to visit Week 26
- The percentage of subjects in each treatment group with confirmed positive AIA at baseline and at least a 4-fold increase in titers after baseline and up to visit Week 26
- The mean change from baseline in each treatment group in AIA titers after baseline and up to visit Week 26. Though not specified in the protocol, this analysis is planned for the subset of subjects with confirmed positive AIA at baseline
- The percentage of subjects in each treatment group with confirmed positive AIA after baseline and up to visit Week 26 who develop any anti-insulin neutralizing antibodies after baseline and up to visit Week 26
- The percentage of subjects in each treatment group with confirmed positive AIA after baseline and up to visit Week 26. This summary is planned to include all subjects regardless of subject's status of AIA at baseline

6.3.2 Safety

- The incidence and severity of all treatment-emergent adverse events (TEAE) and the following subgroups:
  - Hypoglycemia, which will be fully documented in the Hypoglycemic Events Record, using data from subject report (symptomatic), FBG from central lab, study issued glucometer and CGM
  - SAEs, including fatal events
  - Adverse events leading to termination of the study treatment and/or early withdrawal from the study
  - IP-related AEs
  - Injection site reactions
- The incidence of clinically significant laboratory abnormalities
- The incidence of clinically significant abnormalities in electrocardiogram (ECG) and vital signs

6.3.3 Efficacy

- The number and percentage of subjects who achieve a FBG test result of ≤ 8.0 mmol/L (≤ 144.0 mg/dL) at visit Week 26
- The number and percentage of subjects who achieve a HbA1c of < 7.0% at visit Week 26

6.4 Exploratory Endpoints

- Retrospective CGM hypoglycemic rate
- Time in hypoglycemia and hyperglycemia event based on CGM data

7. Definitions

7.1 General

1) Actual Treatment

The actual treatment received is defined as the IP treatment the subject received during the study, regardless of the treatment the subject was allocated to by randomization. If a subject receives both Gan & Lee Insulin Glargine Injection and Lantus® during the study period for whatever reason, then the actual treatment will be based on the treatment taken on the majority of days during the study.

2) Assessment after EOT

Assessment after EOT is defined as AIA/HbA1c assessment documented after date of EOT visit. If date of EOT visit is missing it is defined as assessment documented after date of last dose of IP + 1 day (to consider assessments of subjects who perform the visit assessment before daily dose of IP).

3) Average Daily Dose of IP

Average Daily Dose is defined as captured on the Average Daily Dose of Study Drug CRF page.

4) Baseline

For each endpoint of interest, unless otherwise noted, the study baseline is defined as the last non-missing assessment taken prior to or on the date of the first dose of study IP. For subjects whose treatment assignment is randomly assigned but not dosed after the randomization visit, the baseline is defined as the last non-missing assessment prior to or on the date of randomization.

5) **Change from Baseline**

Change from baseline is defined as (value at post-baseline visit – value at baseline).

6) Completer Week 26

A subject is defined as a Completer Week 26 if the answer to the question "Did the subject complete the study?" is "Yes" on the End of Study CRF page and who received IP for at least 22 weeks.

7) Dates of First and Last Dose

The date of first dose of IP is defined as the date of first dose of IP documented on the First Dose of Study IP CRF page and the date of last dose of IP is defined as the date of last dose of IP documented on the End of Study 2 CRF page. If no date of first dose of IP is available, the date of randomization will be selected as the date of first dose of IP. If no date of last dose of IP is available, the date of completion/discontinuation documented on the End of Study CRF page will be selected as the date of last dose. If date of last dose of IP is not available and subject is lost to follow up based on End of Study CRF page, date of last scheduled visit or date of last telephone contact where an average daily dose is recorded, will be used as the date of last dose of IP.

8) Diabetes Disease Duration

The duration of diabetes is defined as the number of years from the date of original diagnosis of Type 2 Diabetes Mellitus to the date of randomization (presented in full years):

(date of randomization – date of Type 2 diagnosis + 1)/365.25

If the date of Type 2 Diabetes Mellitus is partially missing, then the following imputation rules will be applied:

- Missing day, but month and year are present: the day will be imputed as the 1st of the month.

- Missing day and month but year is present: the day and month will be imputed as July 1 or date of consent, whichever is earlier.
- Date completely missing: no imputation will be done, and diabetes disease duration will also be missing.

9) Dosing Regimen

- Daily (QD): Dosing where the answer to the question "Was the subject compliant with QD dosing since the previous visit?" is Yes on all Average Daily Dose of Study Drug CRF pages.
- Twice daily (BID): Dosing at least once where the answer to the question on the Average Daily Dose of Study Drug CRF page "Was the subject compliant with QD dosing since the previous visit?" is No and "Subject dosed BID on one or more days" is ticked at least once.

10) Double Average Daily Dose

Double Average Daily Dose is defined as having at least double the average daily dose compared to the first average daily dose after randomization at any subsequent average daily dose assessment.

11) Eligibility-Related Important Protocol Deviation (ERIPD)

Eligibility-related important protocol deviations are important protocol deviations coded to the Inclusion Criteria or Exclusion Criteria categories (refer to Appendix 4 for details).

12) End of Treatment visit

The End of Treatment visit (EOT) is defined as the visit Week 26. Any subject who discontinues from treatment before visit Week 26 will have the Visit 9 procedures performed for their EOT visit.

13) Exposure

- Duration of therapy (presented in weeks with one decimal place)

Duration of therapy is defined as (date of last dose – date of first dose + 1)/7.

- Estimated total cumulative dose (presented in U with one decimal place)

The estimated total cumulative dose for a given subject will be calculated using the following formula:

$$\sum_{i=2}^{n_c} (Number\ of\ Days\ between\ \ C_i\ and\ C_{i-1}) * Average\ Daily\ Dose_i$$

where C_i represents the subject's i^{th} contact (including clinic visits as well as telephone contacts) and n_c represents the number of contacts for the given subject. Missing data will not be imputed.

14) Imputation of start and stop dates of AEs (for determination if TEAE only) and prior and concomitant medication (for determination of prior and concomitant only):

- **Start Date**: If only 'day' is missing, and the month and year are not the same as the date of first dose of IP, then impute day with '01'. Otherwise, if the month and year are the same as the date of first dose of IP, use the date of first dose of IP. If 'day' and 'month' are missing, and 'year' is not missing, then impute month and day with month and day of the date of first dose of IP (assuming same 'year'). Otherwise, if year is not the same year, then impute day and month with January 1st. If the start date is completely missing, it will be set to the date of first dose of IP. For prior and concomitant medication if the start date is completely missing and "Was the medication/therapy taken prior to the study (informed consent signature)?" is answered "Yes", no imputation will be done.
- **Stop Date**: If only 'day' is missing, impute day with last day of the month. If 'day' and 'month' are missing, and 'year' is not missing, then impute month with '12' and day with '31' (or date of study discontinuation/completion if the year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs and prior and concomitant medications.

15) Menopausal Status

Menopausal status is defined as either pre-menopausal if the answer to "If female, is the subject of childbearing potential?" is Yes and post-menopausal if the answer is No on Demographics CRF page.

16) Obese

Obese is defined as having a body mass index (BMI) of 30.0 or greater and non-obese is any BMI less than 30.0.

17) Other Anti-diabetes Medications (OAM)

An OAM is defined as any medication from the Prior/Concomitant Medications CRF page where the answer to the question "Was this medication an Other Anti-diabetic Medication?" is Yes and the route is Oral.

18) Overall Subject Average Daily Dose

Overall Subject Average Daily Dose (OSADD) is defined as the average of all non-missing average daily doses recorded throughout the study after randomization (including scheduled and unscheduled assessments). The study diagram shows that the number of Average Daily Dose assessments is scheduled to be collected at seven in-person visits and 5 telephone visits for each subject (See Section 8 of the Protocol).

19) Overdose

Overdose is identified based on investigator discretion, as recorded in the Overdose CRF page. Overdoses are further classified as being related to an adverse event and as being related to a hypoglycemic event in the Overdose CRF page.

Overdose is also identified programmatically as double average daily dose (see above definition), based on information collected in the Exposure CRF page.

Additionally, hypoglycemic events associated with overdose are captured in the Hypoglycemia CRF page.

20) Previous Exposure to Lantus®

Previous Exposure to Lantus® is defined as No Previous Exposure if no Lantus® treatment is documented within 6 months prior to first dose of IP on the prior/concomitant medications CRF page and as Previous Exposure if at least one dose of Lantus® is documented within 6 months prior to first dose of IP (between and including study day -182 and study day -1).

21) Prior and Concomitant Medications

Prior medications are defined as those with a start date prior to the date of randomization and an end date on or before the date of randomization.

Concomitant medications are defined as those ongoing at the date of randomization or with a start date on or after the date of randomization.

22) Study Day

Study Day 1 is defined as the date of first dose of IP. For subjects whose treatment assignment is randomly assigned but not dosed, Study Day 1 is defined as the date of randomization assignment. For dates prior to Study Day 1, the Study Day is calculated as:

Study Day = (Date of Interest/Assessment – Date of Study Day 1)

For dates post Study Day 1,

Study Day = (Date of Interest/Assessment – Date of Study Day 1 + 1)

23) Study Completers

Subjects with non-missing baseline and scheduled visit Week 26 assessment of AIA and who received IP for at least 22 weeks will be used for the analysis.

24) Thyroid Function Abnormality

Thyroid Function Abnormality is defined as any post-baseline thyroid-stimulating hormone (TSH) or free thyroxine (T4) from the central laboratory that is outside the normal range.

25) Time from First Dose of IP to Early Treatment Discontinuation

The time from first dose of IP to early treatment discontinuation will be defined as:

(date of last dose of IP – date of first dose of IP + 1)

Subjects who completed the study will be censored at the date of last dose of IP or study day 182 (Week 26).

26) Treated with IP

All randomized subjects satisfying any of the following criteria will be considered as having received any IP:

- for whom a date of first dose of IP is documented on the First Dose of Study IP CRF page or
- for whom a date of last dose of IP is documented on the End of Study CRF page or
- for whom an average daily dose is documented on the Average Daily Dose of Study Drug CRF page

will be considered as having received any IP. Subjects not satisfying any of the above criteria will be considered as having not received any IP.

27) Visit Window Week 12/26

Visit windows for visit Week 12 and 26 are defined as:

- visit Week 12 ± 1 week (Study Day 84 ± 7)
- visit Week 26 ± 4 weeks (Study Day 182 ± 28).

7.2 Immunogenicity

Blood samples taken from the subjects throughout the study will undergo three-tiered testing. Initially, they will be screened for AIA. Samples with a result falling above a pre-specified threshold will be deemed 'screened positive', otherwise they will be reported as 'negative'. The samples that were "screened positive" will be subsequently tested in the confirmatory assay and will be reported as either 'negative' or 'confirmed positive'. Finally, if found to be 'confirmed positive', samples will then undergo AIA titer analysis in which the sample is diluted until it crosses the specific cut-point, which allows for semi-quantification. In addition, the confirmed positive samples will be tested for neutralizing activity within the neutralizing assay.

1) Confirmed Positive AIA

A subject is deemed to have confirmed positive AIA at a timepoint if both, the screening assay and the confirmatory assay at that timepoint have a positive result, as described above. A subject can have a confirmed positive AIA at any timepoint, including baseline.

2) Negative AIA

A subject is deemed to have negative AIA at a time point if the screening assay at that time point has a negative result. A subject can have a negative AIA at any time point, including baseline.

3) Newly Confirmed Anti-insulin Neutralizing Antibody (NAb)

A subject is deemed to have developed newly confirmed NAb if the subject has a negative AIA at baseline and a confirmed positive AIA after baseline and up to visit Week 26 and has developed anti-insulin neutralizing antibodies after baseline and up to visit Week 26 at any post-baseline measurements.

4) Newly Confirmed Positive AIA

A subject is deemed to have developed a newly confirmed positive AIA if the subject has a negative AIA at baseline, and a confirmed positive AIA after baseline and up to visit Week 26.

5) Important increase in AIA titers

An important increase in AIA titers is defined for subjects who have a (1) confirmed positive AIA at baseline and (2) a non-missing baseline and post-baseline titer analysis,. and the ratio of post-baseline titer to baseline titer is greater than or equal to 4.

6) Treatment-Induced AIA

Treatment-Induced AIA (primary endpoint) is defined as one of the following:

- Newly Confirmed post-baseline positive AIA (in baseline negative)
- Important increase in AIA titers (in baseline positive and with 4-fold increase in titers; post-baseline-to-baseline ratio.)

7.3 Safety

1) American Diabetes Association (ADA) Severe Hypoglycemic AE

A hypoglycemic AE will be classified as "ADA severe" if the answer to the question "Was third party intervention required for this episode of hypoglycemia?" is Yes on the Hypoglycemia CRF page as mentioned in the ADA hypoglycemia position statement (3).

ADA Severe Hypoglycemic AE should not be confused with hypoglycemia AEs that are graded severe (Grade 3) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade (see Section 11.8.1.1).

2) Adverse Event Leading to Discontinuation of IP

An AE will be classified as an AE leading to discontinuation of IP if the answer to the question "Did the adverse event cause the subject to be discontinued from the study?" is Yes on the AE CRF page.

3) Hypoglycemic AE

An AE will be classified as a hypoglycemic AE if the answer to the question "Is this a hypoglycemic event?" is Yes on the AE CRF page.

4) Injection Site Reactions

Injection site reactions will be identified using the High Level Term = "Injection site reactions".

5) IP-related adverse events

An AE will be classified as related to IP if the relationship to study treatment is Possibly Related, Probably Related, or Definitely Related. Additionally, if the relationship is missing, then the AE will be deemed related to IP.

6) Measured Hypoglycemic AE

A hypoglycemic AE will be classified as measured if the lowest blood glucose value documented on the Hypoglycemia page is less than or equal to 3.0 mmol/L.

7) Persistent/Non-persistent Hypoglycemic AE

Hypoglycemic event with Time in hypoglycemia (see definition in Section 7.4) greater or equal to an hour (per CGM) would be classified as persistent. A hypoglycemic event with Time in hypoglycemia below an hour (per CGM) would be classified as non-persistent.

8) Symptomatic Hypoglycemic AE

A Hypoglycemic AE will be classified as symptomatic if the answer to the question "Was subject aware of symptoms?" is Yes on the Hypoglycemia CRF page.

9) Treatment-emergent adverse events (TEAE)

A TEAE is defined as an AE occurring on or after the date of the subject's first dose of IP and on or before the day of last dose for AEs but not more than 30 days after the subject's last dose of IP for SAEs.

7.4 Exploratory

1) Continuous Glucose Monitoring Device Day of Wear

The Day of wear will be defined as starting exactly (x-1)*24 hours and ending x*24 hours after the time of the first assessment at the given visit, where x is the Day of wear from 2 to 8 days.

2) Time in hypoglycemia

The time in hypoglycemia will be defined using the CGM data from days 2 through 8 of wear at each of the 3 visits where CGMs are applied as the sum of the time where the glucose value is ≤3.0 mmol/L.

$$\sum_{i=1}^{n_T} I_{GC_i}(t_{i+1} - t_i)$$

where I_{GC_i} represents the indication of whether or not the glucose concentration at time i is ≤3.0 mmol/L, t_i represents the i^{th} time point (the difference between each time point will be 15 minutes), and n_T represents the number of time points for a given subject and visit and can vary based on subject and visit.

3) Time in hyperglycemia

The time in hyperglycemia will be defined using the CGM data from days 2 through 8 of wear at each of the 3 visits where CGMs are applied as the sum of the time where the glucose value is ≥8.9 mmol/L.

$$\sum_{i=1}^{n_T} I_{GC_i}(t_{i+1} - t_i)$$

where I_{GC_i} represents the indication of whether or not the glucose concentration at time i is greater than or equal to 8.9 mmol/L, t_i represents the i^{th} time point (the difference between each timepoint will be 15 minutes), and n_T represents the number of time points for a given subject and visit and can vary based on subject and visit.

4) Time in euglycemia

The time in euglycemia will be defined using the CGM data from days 2 through 8 of wear at each of the 3 visits where CGMs are applied as the sum of the time where the glucose value is >3.0 mmol/L and < 8.9 mmol/L.

$$\sum_{i=1}^{n_T} I_{GC_i}(t_{i+1} - t_i)$$

where I_{GC_i} represents the indication of whether or not the glucose concentration at time i is >3.0 mmol/L and <8.9 mmol/L, ti represents the ith time point (the difference between each time point will be 15 minutes), and nT represents the number of time points for a given subject and visit and can vary based on subject and visit.

8. Analysis Sets

8.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects whose treatment was randomly assigned. Subjects in the FAS will be grouped according to planned treatment. Most efficacy endpoints will be analyzed using the FAS based on subject's randomized treatment and not administered treatment in case it differs.

8.2 Safety Analysis Set

The Safety Analysis Set (SS) comprises all subjects whose treatment assignment was randomly assigned who receive any IP (defined in Section 7.1), even a partial dose (Gan & Lee Insulin Glargine Injection or Lantus®). Subjects in the SS will be grouped according to the actual treatment received (defined in Section 7.1). Most safety and Immunogenicity endpoints will be analyzed using the SS.

8.3 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPS) comprises all subjects whose treatment was randomly assigned and who received at least 1 partial dose and do not have any important protocol deviations as defined in Section 11.3 up to visit 26 weeks of the study. Subjects in the PPS will be grouped according to actual treatment received. The PPS will be used for some sensitivity analyses (for example, the primary endpoint for immunogenicity [from Section 11.6.1.3] and HbA1c [from Section 11.7.1.3]).

A second Per Protocol Analysis Set (PPS2) will be composed of all subjects whose treatment was randomly assigned, who received at least 1 partial dose and do not have any immunogenicity-interfering important protocol deviations (IIIPD) as defined in Section 11.3 up to visit Week 26. A third Per Protocol Analysis Set (PPS3) will be composed of all subjects whose treatment assignment was randomized, who received at least 1 partial dose and do not have any efficacy-interfering important protocol deviations (EIIPD) as defined in Section 11.3 up to visit Week 26. Subjects in the PPS2 and PPS3 will be grouped according to actual treatment received. The PPS2 and PPS3 are larger and less restrictive analysis sets than the PPS and will be used for some sensitivity analyses for the primary endpoint for immunogenicity [from Section 11.6.1.3] and HbA1c [from Section 11.7.1.3], respectively.

9. Interim Analyses

There are no planned interim analyses for this study.

10. Data Review

10.1 Data Handling and Transfer

All of the data will come from the PRA Health Sciences data management group in SAS® dataset format (SAS version 9.4 or later) converted to Study Data Tabulation Model (SDTM) version 1.4 using SDTM Implementation Guide (SDTMIG) Version 3.2 following the standard Clinical Data Interchange Standard Consortium (CDISC) conventions. Analysis datasets will be created using SAS and following CDISC analysis Data Model (ADaM, version 2.1, Implementation Guide 1.1) Standards.

Medical history and AEs will be coded using MedDRA version 22.0 to assign a system organ class (SOC) and preferred term to each event. Please refer to the Data Management Plan for details.

The following vendors will be providing data:

- PDH: Abbott CGM Data received in mg/dL, will be converted at the analysis stage by dividing with conversion factor of 18.0182 to mmol/L with numbers rounded to the thousandths
- Bioclinica: Randomization assignments (contains unblinding information)
    - True randomization assignments will not be loaded into SAS until the time of unblinding for the final analysis.
- Eurofins: Central Laboratory
- WuXi: Immunogenicity

10.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs and sent to Data Management.

A first dry run around planned last subject follow-up and a second dry run before the final database lock will allow for screening prior to database lock. The second dry run TFLs will be discussed with the sponsor

in a data review meeting with blinded team to identify any data issues and seek corrections prior to the database lock. The PRA statistician and the sponsor must approve the database freeze and the final database lock.

10.3 COVID-related Database Restrictions

As of the date of this SAP version (November 12, 2020), the clinical database contains outstanding queries that could not be reconciled due to permanent site closure and/or COVID-19 related site restrictions. All subject follow-up had completed before permanent site closure or COVID-19 site restrictions were imposed; therefore, subject safety was not affected. Each of these irreconcilable data points were reviewed by cross-functional team leads, including the PRA lead statistician and the PRA medical monitor. That review found that (a) less than 1% of the subjects were associated with an irreconcilable data point (b) no PD were related to COVID-19 given that the date of last patient follow-up was on August 13, 2019, (c) the influence of the interpretation of key immunogenicity, efficacy and safety endpoints was judged to be minimal. During the remaining data monitoring activities, some of which are remote, additional resolution will continue to complete data reconciliation. These efforts will be documented as part of the database lock process and a complete listing of irreconcilable data will be provided.

11. Statistical Methods

In general, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Continuous variables will be summarized using the number of observations (n), mean, and standard deviation, median, minimum, 25th, and 75th percentiles, and maximum. The median, minimum, 25th, and 75th percentiles, and maximum values will be displayed to the same level of precision as the raw data, the mean to a further decimal place and the standard deviation to two additional decimal places to a maximum of four. All summaries will be presented by treatment groups as well as the total if not mentioned otherwise. Tables presented by scheduled time point will include scheduled visits: Day 1 (Baseline), Week 2, Week 4, Week 8, week 12, Week 20, and Week 26 (the end of treatment (EOT) visit) where assessment applies.

Any subject who discontinues from treatment before visit Week 26 (Visit 9) will have the Visit 9 procedures performed for their EOT visit. This will be captured in the CRF under visit Week 26 and will be presented by scheduled time point tables together with Week 26 results for subjects who completed the study. Whereas no visit window will be applied for most of the visit, visit window will be considered for Week 12 or 26 visit AIA assessment only (and visit window will be considered for Week 26 visit HbA1c assessment only) if the visit is within the visit window (week 12 ± 1 week or week 26 ± 4 weeks). Subjects are encouraged to come back for assessments at Week 12 and Week 26 even if they have discontinued treatment early.

Subjects treated according to previous protocol version who have data recorded at visits > visit Week 26, will have those data listed only.

11.1 Pooling of Sites

Because the efficacy analyses will not be performed or stratified by site, all sites will be pooled. However, for the safety analysis described in Section 11.8.1, sites with fewer than 8 subjects will be pooled. A table in the demographic section of the appendix (Section 14) will summarize the subjects by pooled-site assignment for this HbA1c safety analysis.

11.2 Subject Disposition

The following information will be summarized for subject disposition in the FAS:

- Number and percentage of subjects in each analysis set

- Number of subjects screened and a breakdown of screen fail reasons
- Number and percentage of subjects randomized in each site
- Number and percentage of subjects randomized by pooled site
- Number and percentage of subjects who completed the comparative portion (Visit 2-9) of the study, together with the number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal by discontinuation category as recorded in the End of Study CRF page
- Time from first dose of IP to early discontinuation (also as a Kaplan-Meier plot)

For subject discontinuation where the reason is recorded as 'Subject withdrawal' or 'Other' in the CRF, additional details could be captured in the clinical trial management system (CTMS) and may be summarized manually and discussed in the clinical study report. The main discontinuation categories captured in the CRF may also be manually summarized in the clinical study report by sub-categories recorded in the CTMS as follows:

- The 'Adverse Event' category may be divided into 'Adverse Event' and 'Death'.
- The 'Withdrawal by Subject' category may be divided into 12 sub-categories: 'Non-IP AE', 'Doctor advice', 'Drug switch', 'Protocol procedures', 'Protocol device', 'Higher hypoglycemia', 'Job related', 'Visit schedule', 'Move', 'Personal reason', 'Weight gain' and 'No information'.

The 'Non-compliance with Protocol' category may be divided into 'Protocol non-compliance' and 'Subject not eligible.'

A listing of subjects' randomization number, and their actual versus randomized treatment group for all the subjects in the FAS will be provided.

11.3 Important Protocol Deviations

Per PRA processes, protocol deviations data will be entered into the CTMS, in accordance with the Protocol Deviation Guidance Document. The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS, without regard to treatment assignment in accordance with the Blinding Plan. The per protocol analysis sets determined by types of important protocol deviation must be finalized at the data review meeting (or earlier), prior to database lock.

Based on the protocol deviations data entered into CTMS, the important protocol deviations thought to potentially impact the statistical analyses or subject safety will be listed and tabulated using incidence and percentages by deviation type and randomized treatment group in the FAS. Important protocol deviations are defined in the Protocol Deviation Guidance document. The last approved version of Protocol Deviation Guidance before the database lock will define the per protocol analysis sets.

1) Immunogenicity-Interfering Important Protocol Deviations (IIIPD)

Important Protocol Deviations are subdivided into those that are thought to interfere with immunogenicity and those that do not. These immunogenicity-interfering important protocol deviations (IIIPD) are listed explicitly in Appendix 4 and will be used to identify those subjects that are excluded from the Per Protocol Analysis Set 2 (See Section 8.3). This study population will be used in a sensitivity analysis defined in Section 11.6.1.3.

2) Efficacy-Interfering Important Protocol Deviations (EIIPD)

Important Protocol Deviations are classified into those that are thought to interfere with HbA1c and those that do not. These efficacy-interfering important protocol deviations (EIIPD) are listed explicitly in

Appendix 4 and will be used to identify those subjects that are excluded from the Per Protocol Analysis Set 3 (See Section 8.3). This study population will be used in a sensitivity analysis defined in Section 11.7.1.3.

3) Eligibility-Related Important Protocol Deviations (ERIPD)

Eligibility-related important protocol deviations are important protocol deviations violating any inclusion or exclusion criteria (refer to Appendix 4 for details). This indication will be used in sensitivity analyses for immunogenicity, efficacy, and safety measures to evaluate the impact of these important deviations.

11.4 Demographic and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the FAS, SS, and PPS. Descriptive statistics will be provided for age, age group, sex, race, ethnicity, baseline body weight, height, BMI, duration of diabetes, baseline HbA1c, baseline immunogenicity result, and presence/absence of thyroid disease (plus a breakdown of type for subjects with thyroid disease, e.g. hypothyroidism, hyperthyroidism, structural abnormality, or thyroid cancer). A listing will be provided for FAS. Additionally, demographic information and baseline characteristics will be summarized by treatment group and disposition status in the SS.

Medical history conditions will be coded using MedDRA version 22.0. The number and percentage of subjects with each medical history term will be summarized by the MedDRA system organ class (SOC) and preferred term using the FAS.

11.5 Treatments

11.5.1 Prior and Concomitant Medications

Medications received prior and concomitantly with IP, categorized according to WHODRUG (Version 2017SEP DDE+HD [Herbal + Enhanced] B3), will be summarized separately using the FAS. The number and percentage of subjects using each medication will be displayed by WHODRUG defined preferred terms.

A separate summary of concomitant OAM will be presented. Additionally, "Insulins and Analogues" selected by WHODRUG ATC level 3 of "A10A" and categorized by ATC level 4 will be summarized separately for prior and concomitant medications.

11.5.2 Extent of Exposure

For the study IP, summary statistics will be provided for SS for duration of therapy and estimated total cumulative dose and overall subject average daily dose (OSADD; defined in Section 7.1). The number and percentage of subjects who experience at least one overdose (as reported in the Overdose CRF page) as well as the number and percentage of those with double average daily dose at any time during the study (defined in Section 7.1) will be provided.

A separate overall summary of overdoses will provide the total number of overdoses experienced by all subjects, number and percentage of overdoses related to an adverse event, and number and percentage of overdoses related to a hypoglycemic event as recorded on the Overdose CRF. Additionally, a summary table will provide the number and percentage of subjects with at least one overdose event, number and percentage of subjects experienced overdose that is related to a hypoglycemic event as reported on the Hypoglycemia CRF, and also the number and percentage of subjects with an overdose that is related to an SAE as reported in the Adverse Event CRF page.

Additionally, a correlation plot of the average daily dose versus the change from baseline in HbA1c result at the corresponding visit will be presented for FAS.

The difference between treatment groups in the mean OSADD will be estimated along with the corresponding 90% CI in the FAS using analysis of variance with treatment as the only independent variable in the model and reported with a p-value.

A listing of the lot number(s) for each subject and a listing of unique manufacturing lot numbers will be provided. Drug accountability will be listed.

A manual summary of subjects with one or more defective IP pens will be provided and discussed in the clinical study report based on information collected outside of the clinical database. This manual summary will include subject ID, site, investigator name, product quality issue reported, and site / clinical research associate comments.

11.6 Immunogenicity Analyses

All Immunogenicity analysis will be performed using the SS based on all treated subjects.

11.6.1 Primary Endpoint

11.6.1.1 Incidence of Treatment-Induced Anti-Insulin Antibodies

Incidence of treatment-induced AIA is defined as subjects develop newly confirmed positive AIA or have important (4-fold) increase in AIA titer up to visit Week 26. The objective of the primary immunogenicity analysis will be to evaluate equivalence of Gan & Lee Insulin Glargine Injection to Lantus® by comparing the limits of the 90% confidence interval (CI) of difference in proportion of treatment-induced AIA development to the specified margins (-margin, +margin) where the margin is dependent on the unadjusted treatment-induced AIA rate in Lantus® and is defined in Section 5.1, Table 3.

The estimand of interest for the primary immunogenicity analysis is the difference in treatment-induced AIA rates regardless if all subjects tolerate or adhere to study treatment or receive other insulin treatments. Intercurrent events will be handled according to the treatment policy strategy. Treatment Policy strategy is defined as the strategy that considers "The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs" (See ICH E9 R1 addendum). All AIA data collected, scheduled and unscheduled, will be considered for the analysis, even if collected after the occurrence of intercurrent events of (1) discontinuing study treatment, (2) returning to initial treatment and/or (3) initiating a new treatment.

Any treatment-induced AIA after baseline and up to visit Week 26 will have the subject count as treatment-induced AIA for the primary endpoint. For subjects who have no AIA measurement at scheduled visit Week 12 or 26, AIA measurements from returned visits that fall within the allowed visit window (visit Week 12 ± 1 week or visit Week 26 ± 4 weeks, defined in Section 7.1) will be assigned to the respective time point.

Missing data will be handled as described in Section 11.6.1.2. The SS will be used for the primary analysis.

The number and percentage of subjects in each treatment group who develop treatment-induced AIA as defined in Section 7.2 after baseline and up to visit Week 26 (upper limit of the visit window) will be evaluated using a logistic regression model in proportions along with the corresponding 90% CI.

Equivalence in difference in proportion δ between Gan & Lee Insulin Glargine Injection (π_1) and Lantus® (π_2) will be tested by comparing the limits of the 90% CI for treatment-induced AIA development with the following null hypothesis:

$$H_0: (\pi_1 - \pi_2) \leq -\delta_0 \; or \; (\pi_1 - \pi_2) \geq \delta_0$$

Against the alternative hypothesis of:

$$H_1: -\delta_0 < (\pi_1 - \pi_2) < \delta_0$$

where δ_0 is the margin dependent on the observed unadjusted treatment-induced AIA rate in Lantus® (π_2) and is defined in Section 5.1, Table 3.

To evaluate equivalence of Gan & Lee Insulin Glargine Injection to Lantus® the calculated 90% CI has to be entirely contained with the interval $(-\delta_0, \delta_0)$.

A sample SAS code fragment is provided below for reference:

```
proc logistic data=<data>;
        class trt / param=ref ref='Lantus';
        model response=trt;
run;
```

The Fisher scoring algorithm will be used for maximum likelihood estimation of the regression parameters. The difference in proportions along with the corresponding 90% CI in the SS using a logistic regression model will be calculated. The delta method will be used to calculate the standard error for the difference and the associated confidence interval (Ge M, Durham LK, Meyer RD 2011 (4)).

Subjects were randomly assigned to treatment using variable block size (See Section 5.2). Blocking should be taken into account when the intra-block correlation is non-zero (Matts and Lachin 1988 (5)). An intra-block correlation of zero can be safely ignored in the analysis (Efird 2011 (6)). Subjects are generally anticipated to remain within sites so the intra-block correlation within investigative site can be assumed to be zero and therefore no adjustment for block is planned.

11.6.1.2 Methods for Handling Dropouts and Missing Data

Utilizing a "Treatment Policy" strategy, missing data (after using data collected during or after treatment, and assigning data to the appropriate scheduled visit as described above) for the primary endpoint will be imputed as per Table 4. Sites have been trained in the importance of collecting baseline AIA samples. In the rare and unlikely event a site does not collect a baseline AIA sample, imputation rule for missing baseline assessment is included in the table. Unscheduled assessments (e.g. EOT documented at visit Week 26 outside the visit windows for discontinued subjects) up to visit Week 26 will be considered in the overall result but will not be imputed.

Table 4: Imputation Rules for Missing Data in Primary Immunogenicity Analysis

Category	Sample Availability	Imputation	Likely Scenarios
1	All three AIA samples collected and analyzed	• No imputation	• Subjects complete the study. • Dropout subjects provide the required AIA samples within the defined visit window.
2	At least one AIA sample missing at Week 12 or Week 26 regardless of baseline sample availability	• Subject will be counted as 'developing a treatment-induced AIA'.	• Dropout subjects who are unable to provide AIA samples in respective visit window. • AIA sample missing due to protocol deviations.

Category	Sample Availability	Imputation	Likely Scenarios
3	Baseline sample missing, but both Week 12 and Week 26 samples are collected and analyzed	• Subject will be counted as 'developing a treatment-induced AIA' if any of Week 12 or Week 26 results are positive. • Subject will be counted as 'NOT developing a treatment-induced AIA' if both Week 12 and Week 26 results are negative.	• Baseline AIA sample missing due to protocol deviations.
4	Any positive results from unscheduled (or out of window) AIA sample(s) during the Treatment Period	• Positive result from unscheduled AIA sample will be treated the same way as the Week 12/26 samples when baseline result is present. • Positive result from unscheduled AIA sample will render the subject as 'developing a treatment-induced AIA' if baseline sample is missing.	• Sample collection out of the allowable sample collection window. • Sample collection due to other protocol deviations.

11.6.1.3 Sensitivity Analyses

Inherent in the primary endpoint analysis described above are several implicit assumptions that can possibly affect the generalizability of immunogenicity. There are four assumptions that are important to mention. The primary analysis assumes that the impact on the immunogenicity conclusion of early discontinuations, important protocol deviations, less than full treatment duration and patterned missing data is negligible. Although the scientific rationale to make these assumptions is reasonable, sensitivity analyses for the primary endpoint of immunogenicity to assess the impact of these effects are planned, as follows.

1) Composite Strategy: Subjects in the SS with the intercurrent event of discontinuing treatment will be considered as having a treatment-induced AIA. Results of assessment after the end of treatment are excluded from the analysis. The imputation approach as described in Table 4 will be used for missing data. This sensitivity analysis will examine the assumption that results were not impacted by the discontinuation of treatment (as these will be imputed as positive immune response).

2) Per Protocol Analysis Set (PPS): Subjects with any important protocol deviations (as defined in Section 11.3) will be excluded from the analysis. For subjects in the PPS, the imputation approach as described in Table 4 for primary analysis will be followed. In the primary analysis, subjects with important protocol deviations could falsely draw the estimated treatment difference closer. Exclusion of these subjects in this sensitivity analysis will help assess the magnitude, if any, of this effect.

3) SS - Completers: This analysis will not use any imputation of missing data. Only subjects with valid baseline and visit Week 12 and Week 26 assessments conducted within the required visit window (visit Week 12 ± 1 week and visit Week 26 ± 4 weeks, respectively) and who had treatment until visit Week 26 will be used for the analysis. Subjects with less than a full treatment duration could

underestimate the proportion of subjects reporting positive immune response. By including only completers, as in this sensitivity analysis, this estimated treatment difference is determined only by subjects whose treatment duration was full.

4) Per Protocol Analysis Set 2 (PPS2) - Subjects with any immunogenicity-interfering important protocol deviations (IIIPD; as defined in Section 11.3) will be excluded from the analysis. For the subjects in the PPS2, the imputation approach as described in Table 4 for primary analysis will be followed. In the primary analysis, subjects with immunogenicity-interfering important protocol deviations could falsely draw the estimated treatment difference closer. Exclusion of these subjects in this sensitivity analysis will help assess the magnitude, if any, of this effect.

5) ERIPD Interaction Analysis for immunogenicity – To assess the impact of eligibility related important protocol deviations on the treatment effect for immunogenicity, this analysis will be carried out using an extended model of the main analysis, by including ERIPD (yes/no) and treatment by ERIPD interaction as factors. The interaction parameter estimate, 90% CI and p-value will be presented with number and percentage of subjects in each ERIPD category under each treatment arm.

All these sensitivity analyses will be conducted as described for the primary analysis, using the same margins from the primary analysis.

Additional analyses examining the development of treatment-induced AIA at Week 26 in the following subgroups using the SS with imputation as described in Table 4 for primary analysis will be presented in a forest plot:

- Gender (Male versus Female)
- Age (< 65, versus ≥ 65 years old)
- Race (white versus non-white)
- BMI (Obese versus Non-obese)
- Menopausal Status (Pre- versus post-)
- Dosing Regimen (Twice daily (BID) Dosing at least once versus daily (QD) Dosing)
- Previous Exposure to Lantus® (No previous exposure versus previous exposure (within 6 months prior to study initiation))

11.6.1.4 Multiplicity

Hierarchical testing strategy will be used to account for multiplicity. Equivalence in efficacy will only be demonstrated if equivalence in immunogenicity is demonstrated.

11.6.2 Secondary Immunogenicity Endpoints

All analyses will include on and after study treatment AIA data up to visit Week 26.

11.6.2.1 Subjects with Negative Anti-Insulin Antibodies at Baseline Who Develop Newly Confirmed Positive Anti-Insulin Antibodies

The percentage of subjects in each treatment group with negative AIA at baseline who develop newly confirmed positive AIA after baseline and up to visit Week 26 will be summarized in proportions. The difference in proportions will be estimated along with the corresponding 90% CI in the subset of SS using a logistic regression model.

Missing data will be imputed as described for the primary endpoint in Table 4.

11.6.2.2 Subjects with Important Increase in AIA Titers

The percentage of subjects in each treatment group with confirmed positive AIA at baseline who develop important increase (at least a 4-fold increase) in titers (defined in Section 7.2) up to visit Week 26 will be compared using an difference in proportions. The difference in proportions will be estimated along with the corresponding 90% CI in the subset of SS (with positive AIA at baseline) using a logistic regression model with treatment as the only independent variable in the model.

11.6.2.3 Change in Anti-Insulin Antibody Titer

The change from baseline in AIA titers at visit Week 12 and visit Week 26 will be summarized descriptively in subjects with confirmed positive AIA at baseline. Though not specified in the protocol, this analysis is planned for the subset of subjects with confirmed positive AIA only.

11.6.2.4 Subjects with Confirmed Positive Anti-Insulin Antibodies Who Develop Newly Confirmed Neutralizing AIA

The percentage of subjects in each treatment group with confirmed neutralizing AIA after baseline and up to visit Week 26 will be compared using difference in proportions. The difference in proportions will be estimated along with the corresponding 90% CI in the SS using a logistic regression model with treatment as the only independent variable in the model.

Missing data will not be imputed, the percentages will be based on the subjects with documented confirmed positive AIA after baseline and up to visit Week 26.

11.6.2.5 Subjects with Confirmed Positive Anti-Insulin Antibodies

The percentage of subjects in each treatment group with confirmed positive AIA after baseline and up to visit Week 26 will be compared using difference in proportions. The difference in proportions will be estimated along with the corresponding 90% CI in the full SS using a logistic regression model with treatment as the only independent variable in the model.

Missing data will be imputed as described for the primary endpoint in Table 4.

11.7 Efficacy Analyses

11.7.1 Key Secondary Endpoint

An overview of planned analyses for the key secondary endpoint of change from baseline in HbA1c, including sensitivity analyses, is provided in Table 5 below.

Table 5: Overview of key secondary endpoint analyses

Analysis	Population used	Analysis Details	Section reference
1. Main analysis	Full analysis set	Treatment Policy Estimand - ANCOVA using MI under the assumption of MNAR; this analysis uses unscheduled HbA1c results from discontinued subjects to impute missing in each treatment arm.	Section 11.7.1.1 Change from Baseline in HbA1c at 26 weeks

Analysis	Population used	Analysis Details	Section reference
2. Sensitivity analysis	Per protocol analysis set	ANCOVA using MI under the assumption of MNAR; this analysis uses the same approach for imputation as the main analysis. Used to assess the robustness of main analysis to important deviations from the protocol.	Section 11.7.1.3 Sensitivity Analyses - PPS
3. Sensitivity analysis	Full analysis set of completers	ANCOVA without imputation. This analysis is used to assess the robustness of main analysis to subjects lost to follow-up.	Section 11.7.1.3 Sensitivity Analyses - FAS completers
4. Sensitivity analysis	Per protocol analysis set 3	ANCOVA using MI under the assumption of MNAR; this analysis uses the same approach for imputation as the main analysis. In the main analysis, subjects with efficacy-interfering deviations could falsely draw the estimated treatment difference closer. Exclusion of these subjects in this sensitivity analysis will help assess the magnitude, if any, of this effect.	Section 11.7.1.3 Sensitivity Analyses - Per Protocol Analysis Set 3
5. Sensitivity analysis	Full analysis set	Treatment Policy Estimand – MMRM will include all longitudinal HbA1c data points measured.	Section 11.7.1.3 Sensitivity Analyses - Mixed Model Repeated Measure
6. Sensitivity analysis	Full analysis set	ANCOVA using MI under the assumption of MNAR. This analysis uses unscheduled HbA1c results from discontinued subjects to impute missing in each treatment arm, with the addition of the term of presence/absence of ERIPD main effect and an interaction term of treatment*ERIPD.	Section 11.7.1.3 Sensitivity Analyses – ERIPD Interaction Analysis for Efficacy
7. Sensitivity analysis	Full analysis set	ANCOVA using MI under the assumption of MNAR in each treatment arm for the following subgroups: Gender (male versus female), Age (< 65, versus ≥ 65 years old), Race (white versus non-white), BMI (Obese versus Non-obese), Menopausal Status (Pre- versus post-), Eligibility Criteria Met (Presence of an eligibility-related important protocol deviation versus no presence of an eligibility-related important protocol deviation).	Section 11.7.1.3 Sensitivity Analyses – Subgroup analyses
8. Tipping point analysis	Full analysis set	ANCOVA using MI under progressively severe departures from missing at random (MAR) assumption (i.e. MNAR assumption).	Section 11.7.1.3 Sensitivity Analyses - Tipping point analysis

11.7.1.1 Change from Baseline in HbA1c at 26 weeks (Table 5, Analysis 1)

HbA1c values and change from baseline will be summarized by time point and treatment group.

HbA1c will be measured by a central laboratory in a single site in the US which is National Glycohemoglobin Standardization Program (NGSP) Level 1 certified. The estimand of interest on the HbA1c analysis is the difference in change from baseline for HbA1c using the "treatment policy strategy".

For subjects who discontinue from treatment before visit Week 26 or who have no HbA1c measurement at visit Week 26, HbA1c will be assigned to the scheduled time point if they fall within the allowed visit windows (visit Week 26 ± 4 weeks).

Submissions to Food and Drug Administration (FDA) and European Medicines Agency (EMA) require different methods for efficacy HbA1c evaluation:

For FDA submission, equivalence in change from baseline in HbA1c between Gan & Lee Insulin Glargine Injection (μ_1) and Lantus® (μ_2) will be tested using the two one-sided tests (TOST) approach proposed in Schuirmann (1987) (7) with the following null hypothesis:

$$H_0: (\mu_1 - \mu_2) \leq -0.4 \; or \; (\mu_1 - \mu_2) \geq 0.4$$

Against the alternative hypothesis of:

$$H_1: -0.4 < (\mu_1 - \mu_2) < 0.4$$

with α=0.05.

The 90% CI will be estimated using a pattern mixture model that uses multiple imputation (MI) analyzed using Analysis of Covariance (ANCOVA) with treatment included as a fixed effect and baseline HbA1c included as a covariate. Separately in each treatment group, the imputation will use outcomes in subjects who discontinued treatment prior to Week 26 but returned to provide a visit Week 26 HbA1c sample to impute outcomes in subjects without actual visit Week 26 recorded results under the MNAR assumption. No imputation will be performed for missing baseline HbA1c. Equivalence will be assessed based on the 90% CI; no p-values will be computed. Change from baseline in HbA1c between Gan & Lee Insulin glargine Injection and Lantus® will be considered equivalent if the 90% CI is within the margins (-0.4%, 0.4%).

For EMA submission, non-inferiority in change from baseline in HbA1c between Gan & Lee Insulin Glargine Injection and Lantus® will be tested using the following null hypothesis:

$$H_0: (\mu_1 - \mu_2) \geq 0.4$$

Against the alternative hypothesis of:

$$H_1: (\mu_1 - \mu_2) < 0.4$$

with a 1-sided α=0.025.

In addition, the same non-inferiority test with a margin of 0.3% will be performed.

The 95% CI will be estimated using a pattern mixture model that uses multiple imputation analyzed using ANCOVA with treatment included as a fixed effect and baseline HbA1c included as a covariate. Separately in each treatment group, the imputation will use outcomes in subjects who discontinued treatment prior to Week 26 but returned to provide a visit Week 26 HbA1c sample (labeled as the unscheduled) to impute outcomes in subject without actual visit Week 26 recorded results under the MNAR assumption. No imputation will be performed for missing baseline HbA1c.

Analysis of HbA1c will follow a hierarchical testing strategy: first, non-inferiority will be tested using a margin of 0.4%, and only if this test is significant, then non-inferiority will be tested using a margin of 0.3%.

Non-inferiority will be assessed based on the 95% CI; no p-values will be computed. Change from baseline in HbA1c between Gan & Lee Glargine Injection and Lantus® will be considered non-inferior if the 95% CI is below the margins of 0.4 and 0.3%, respectively.

For both, FDA and EMA submissions, to estimate the CI of the difference in HbA1c, the pattern-mixture model will be fitted using the SAS® procedure "MIXED" for FAS. A sample SAS code fragment is provided below for reference (note: actual seeds to be used in the analysis are presented below):

```
proc mi data=<data> nimpute=50 seed= 359648 out=<out_data>;
        by trt;
        class unscheduled;
        monotone reg(Week26_HbA1c=base_HbA1c);
        mnar model(Week26_HbA1c / modelobs = (unscheduled = '1'));
        var base_HbA1c;
run;
```

In between these steps, the data will be transposed and then the change from baseline at visit Week 26 will be calculated.

```
proc mixed data=<out_data> out=<lsmeans>;
        by _imputation_;
        class trt;
        model CFB_HbA1c_26 = trt base_HbA1c / ddfm=kr;
run;
proc mianalyze data=<lsmeans>;
        by effect;
        modeleffects estimate;
        stderr;
run;
```

11.7.1.2 Methods for Handling Dropouts and Missing Data

Missing HbA1c data at visit Week 26 will be imputed for the analysis on HbA1c using MI method, performed separately for each treatment group.

Additionally, the robustness of primary analysis results under the MNAR assumption will be explored through multiple sensitivity analysis as listed in Table 5 and detailed in Section 11.7.1.

The pattern of missing data for HbA1c will be provided with a context of Week 26 measurement to be "Completed on schedule", "Returned", or "Not returned". This summary arranges the response data into "patterns" (for example, the number and percentage of subjects with no missing data at baseline and visit week 26).

11.7.1.3 Sensitivity Analyses

To evaluate the impact of important protocol deviations and missing data, sensitivity analyses will be performed using the analysis methods described for the FDA equivalence and EMA non-inferiority analyses:

1) PPS: Using MI approach as described for main HbA1c analysis. If in the number of subjects who discontinued treatment and return to provide an HbA1c sample at Week 26 is insufficient to perform the MI, the MI will instead be performed using data from all patients with HbA1c results at Week 26 in each treatment group under the assumption of MNAR (Table 5, Analysis 2).

2) FAS Completers: This analysis will not use any imputation of missing data. Only subjects with valid baseline and visit Week 26 assessment conducted at actual visit Week 26 and who had treatment until visit Week 26 will be used for the analysis (Table 5, Analysis 3).

3) Per Protocol Analysis Set 3 (PPS3) - Subjects with any efficacy-interfering important protocol deviations (EIIPD; as defined in Section 11.3) will be excluded from the analysis. For the subjects in the PPS3, the imputation approach as described for the main analysis will be followed. In the main analysis, subjects with efficacy-interfering important protocol deviations could falsely draw the estimated treatment difference closer. Exclusion of these subjects in this sensitivity analysis will help assess the magnitude, if any, of this effect. (Table 5, Analysis 4)

4) Mixed model repeated measure (MMRM): this sensitivity analysis will include all post-baseline HbA1c measures from each time point as the dependent variable. The independent variables in the model include fixed effects for treatment assignment (2 levels), time (3 post-baseline times), treatment-by-time interaction, and covariate terms for the baseline HbA1c score and baseline HbA1c score-by-time interaction (which allows the effect of baseline covariate parameter to change over time). An unstructured covariance matrix will be used to model the inter-dependencies among the repeated measures. However, if the model does not converge, an alternative covariance matrix will be used which is appropriate for the repeated measurements (e.g., first-order autoregressive). Given the missing data, the Kenward-Roger approximation will be used for calculating the denominator degrees of freedom and adjusting standard errors. If a structured variance-covariance matrix is used, sandwich estimator will be used to estimate the variance of the treatment effect estimate. The FAS will be used to generate the results. (Table 5, Analysis 5)

The SAS code to be used for the repeated measure model is:

```
Proc mixed data=<data>;
        class trt visit subject;
        model HbA1c = trt
                      visit
                      trt*visit
                      base_HbA1c
                      base_HbA1c*visit
                      / solution ddfm=kr;
        repeated visit / subject = subj type=un;
        lsmeans treatment*visit / pdiff cl;
run;
```

5) ERIPD Interaction Analysis for Efficacy – To assess the impact of eligibility related treatment effect on efficacy, this analysis will be a repeat of the main analysis with the addition of the term of presence/absence of ERIPD main effect and an interaction term of treatment*ERIPD. The parameter estimate of the interaction term, 90% CI and p-value will be presented with least square means estimated for each ERIPD group under the treatment arms. (Table 5, Analysis 6)

Additional analysis examining the change from baseline in HbA1c at visit Week 26 in the following subgroups will be presented in a table and a forest plot, by treatment groups but not overall. Missing outcomes were imputed separately in each treatment group using outcomes in subjects who completed the study. These analyses will be conducted according to the FDA submission approach (i.e. 90% CI and 0.4% margin) with MI for the FAS (Table 5, Analysis 7):

- Gender (Male versus Female)
- Age (< 65 versus ≥ 65 years old)
- Race (white versus non-white)
- BMI (Obese versus Non-obese)
- Menopausal Status (Pre- versus post-)
- Eligibility Criteria Met (Presence of an eligibility-related important protocol deviation versus no presence of an eligibility-related important protocol deviation). Eligibility-related important protocol deviations are those coded to the Inclusion Criteria or Exclusion Criteria categories (refer to Appendix 4 for details).

Additionally, tipping point analyses with MI approach will be conducted for analyses of change from baseline in HbA1c at visit Week 26 in FAS for both FDA equivalence (2-way tipping point) and EMA non-inferiority submissions. For the MI approach, each missing value will be replaced with a set of plausible values that represent the uncertainty about the right value to impute (Table 5, Analysis 8).

Tipping point analyses evaluate varying combinations of imputed missing data values with added penalties of shift values until the analysis reaches a "tipping point", or more specifically the point at which the study's conclusions of equivalence or non-inferiority for HbA1c would change as summarized by the confidence intervals. This sensitivity analysis will explore the effect of the violation of the MAR assumption and will instead examine the results under a MNAR assumption. If the tipping point analysis reveals that the "tipping point" is at an unreasonable shift, then the robustness of the study results under the MAR assumption are supported.

A sample SAS code fragment is provided below for reference (note: actual seeds to be used in the analysis are presented below):

```
proc mi data=<data> nimpute=10 seed= 120920 out=<out_data> minimum=. 0 0;
        class trt;
        monotone reg;
        mnar adjust(week_26 /shift = <shift> adjustobs=(trt='Gan & Lee Insulin Glargine Injection'))
             adjust(week_26 /shift = -<shift> adjustobs=(trt='Lantus'))
        var trt base_HbA1c week_26;
run;
```

The following shift values will be used (increase for Gan & Lee Insulin Glargine Injection and decrease for Lantus® simultaneously): 0, 0.2, 0.4, etc. until the conclusion of equivalence or non-inferiority will change, the equivalence 2-way tipping point analysis utilizes a shift in both directions (additionally decrease for Gan & Lee Insulin Glargine Injection and increase for Lantus®). The ANCOVA analyses will be performed as described in Section 11.7.1.1.

11.7.2 Secondary Efficacy Endpoint

11.7.2.1 Proportion of Subjects Achieving Glycemic Control

The following secondary efficacy variables will be analyzed using the 90% CI of difference of proportions:

- The number and percentage of subjects who achieve a FBG test result of ≤ 8.0 mmol/L (≤ 144.0 mg/dL) at visit Week 26
- The number and percentage of subjects who achieve a HbA1c of < 7.0% at visit Week 26.

The difference in proportions will be estimated along with the corresponding 90% CI in the FAS using a logistic regression model. Only measurements under treatment will be considered. Subjects without values available at week 26 will be considered as having not achieved glycemic control.

Additionally, number and percentages of subjects who achieve an FBG test result of ≤ 8.0 mmol/L (≤ 144.0 mg/dL) and number and percentages of subjects who achieve a HbA1c of < 7.0% will be presented by time point and treatment group.

11.7.3 Exploratory Variables

11.7.3.1 Retrospective Hypoglycemic Rate

In addition to the analysis of hypoglycemic events from the AE data, a retrospective analysis of the CGM data will be performed to identify hypoglycemic events that may have gone unnoticed by the subject (Table 6, Analysis 1). A retrospective CGM-hypoglycemic event will be defined as anytime the glucose concentration decreases below the threshold of ≤ 3.0 mmol/L. This definition is supported by Seaquist et al (8). Multiple hypoglycemic events while a subject is wearing the CGM device may occur and are defined as having a glucose concentration that returns to > 3.0 mmol/L before decreasing below the threshold again. The number of hypoglycemic events detected between days 2 through 8 of CGM wear for each subject at each visit will be summarized descriptively in the SS. A listing of the CGM-hypoglycemic events including the lowest glucose concentration during the event will be provided.

11.7.3.2 Retrospective Time in Hypoglycemia/Hyperglycemia

The time in hypoglycemia/hyperglycemia/euglycemia will be summarized with descriptive statistics at each visit and overall using the SS (Table 6, Analysis 2).

11.7.3.3 Laboratory-Grade Hyperglycemia

Laboratory-Grade Hyperglycemia (LGH) is defined for any subject whose FBG result is strictly greater than 13.9 mmol/L (250 mg/dL). FBG is scheduled to be collected twice before randomization and at seven instances after randomization. The difference between treatment groups in the proportion of subjects who at any post-randomization time point with LGH will be estimated along with the corresponding 90% CI in the FAS using a logistic regression with treatment as the only independent variable in the model and reported with a p-value.

In addition, the number of incidences of LGH for each subject between visits 3 and 9 (post-randomization) will be counted. The difference between treatment groups in the mean number of LGH events will be estimated along with the corresponding 90% CI in the FAS using analysis of variance with treatment as the only independent variable in the model and reported with a p-value.

11.8 Safety Analyses

Most safety analyses will be performed on the safety analysis population based on subject's actual treatment received.

A listing of planned summaries and analyses evaluating hypoglycemic events along with corresponding analysis plan section references is provided in Table 6.

Table 6: Listing of hypoglycemic event summaries and analyses

Analysis description	Section Reference	Tables Associated
1. Retrospective Summary of Continuous Glucometer Monitoring (CGM): Hypoglycemia Events	Section 11.7.3.1	Table 14.3.3.4.1
2. Retrospective Analysis of Continuous Glucometer Monitoring (CGM): Time in Hypoglycemia/Hyperglycemia	Section 11.7.3.2	Table 14.3.3.4.2
3. Overall Summary of Treatment-Emergent Adverse Events	Section 11.8.1	Table 14.3.2.1
4. Hypoglycemic Treatment-Emergent Adverse Events by Preferred Term	Section 11.8.1	Table 14.3.2.5

Analysis description	Section Reference	Tables Associated
5. Hypoglycemic Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade (based on lowest blood glucose values measured by fingerstick or venous blood draw)	Section 11.8.1.1	Table 14.3.2.6.1
6. Hypoglycemic Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade (based on lowest blood glucose values measured by test method equal "Other")	Section 11.8.1.1	Table 14.3.2.6.2
7. Hypoglycemic Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum ADA Grade (based on lowest blood glucose value measured by fingerstick or venous blood draw)	Section 11.8.1.1	Table 14.3.2.6.3
8. Hypoglycemic Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum ADA Grade (based on lowest blood glucose values measured by test method equal "Other")	Section 11.8.1.1	Table 14.3.2.6.4
9. Severe Hypoglycemic Treatment-Emergent Adverse Events by Preferred Term	Section 11.8.1	Table 14.3.2.7
10. Serious Hypoglycemic Treatment-Emergent Adverse Events by Preferred Term	Section 11.8.2	Table 14.3.2.13
11. IP-Related Serious Hypoglycemic Treatment-Emergent Adverse Events by Preferred Term	Section 11.8.2	Table 14.3.2.14
12. Summary of Hypoglycemic Treatment-Emergent Adverse Events	Section 11.8.1	Table 14.3.3.2.17
13. Summary of Symptomatic or Measured Hypoglycemic Treatment-Emergent Adverse Events by Site	Section 11.8.1.1	Table 14.3.3.2.18
14. Analysis of Hypoglycemic Treatment-Emergent Adverse Events	Section 11.8.1	Table 14.3.3.2.19
15. Summary of Reported ADA Hypoglycemic Treatment-Emergent Adverse Events	Section 11.8.1.1	Table 14.3.3.2.20
16. Overall Summary and Analysis of Treatment-Emergent Adverse Events by ERIPD Subgroup in SS, PPS2, and PPS3		Table 14.3.2.21; 14.3.2.22; 14.3.2.23; 14.3.2.24
17. Maximum Post-baseline Fasting Glucose CTCAE Grade	Section 11.8.3.1	Table 14.3.3.4.16

11.8.1 Treatment Emergent Adverse Events

An overall summary of TEAEs (defined in Section 7.3) will be presented, including the number of events reported, the number and percentage of subjects with at least one of the following (Table 6, Analysis 3):

- Adverse event
- Grade ≥ 3 TEAE
- Hypoglycemic TEAE
- Severe hypoglycemic TEAE
- IP-related AE

- Grade ≥ 3 IP-related AE
- Death
- SAE
- IP-related SAE
- Hypoglycemic SAE
- AE leading to discontinuation of IP
- IP-related AE leading to discontinuation of IP

To evaluate the potential impact of eligibility related important protocol deviations on subject safety, an overall summary of TEAEs will also be presented by presence / absence of ERIPD. ERIPDs are those coded to the Inclusion Criteria or Exclusion Criteria categories (refer to Section 7.1, 11.3 and Appendix 4 for details). Additionally, safety analyses of ERIPD interaction with treatment group will be performed in logistic regression models adjusted by country. The interaction term estimates, 90% CI and p-value from these interaction analyses will be presented with the number and percentage of subjects with the following TEAEs by presence / absence of ERIPD under each treatment arm:

- Adverse event
- Grade ≥ 3 AE
- Hypoglycemic AE
- Severe hypoglycemic AE

A fragment of the SAS code for the interaction analysis is provided below for reference.

```
proc logistic data=<data>;
        class trt ERIPD/ param=ref ref='Lantus';
        model response=trt ERIPD trt*ERIPD;
run;
```

A breakdown of the number and percentage of subjects reporting each AE, categorized by System Organ Class (SOC) and preferred term coded according to MedDRA, will be presented. Note that counting will be by subject (not event), and subjects are counted only once within each SOC or preferred term. Sorting will be in descending frequency for SOC and descending frequency for preferred term within SOC in the total column.

A summary of events reported, categorized by maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) severity grade as reported in the CRF will also be provided. Subjects with multiple events within a particular SOC or preferred term will be counted under the category of their most severe event within that SOC or preferred term. Sorting will be in descending frequency for SOC and descending frequency for preferred term within SOC in the total column.

Subject incidence of the following TEAEs will be tabulated by preferred term in descending order of frequency in the total column:

- Grade ≥ 3 AEs
- Hypoglycemic AEs
- Severe hypoglycemic AEs
- IP-related AEs
- Grade ≥ 3 IP-related AEs
- AE leading to discontinuation of IP
- IP-related AE leading to discontinuation of IP
- Injection site reactions

A forest plot of the difference in incidence rates and CIs of TEAEs preferred terms with a ≥ 5% difference in incidence between groups will be summarized. The 90% CIs will be computed using Wald method for risk difference without continuity correction.

Additionally, the hypoglycemia event rate will be compared between treatment groups using a negative binomial regression model (Table 6, Analysis 14). The response variable in the model will be the number of hypoglycemia events. The model will include factors for treatment group and site. In this study, sites were found to use variable procedures in their determination, collection and recording of the number of hypoglycemia episodes for individual subjects. So, to account for this additional variation, SITE is planned to be included as a fixed factor in the negative binomial regression model. This model will allow estimation of the site-adjusted, two-sided, 95% confidence interval of the treatment contrast. If that CI includes zero, we will conclude that this study does not provide sufficient evidence that subjects on this biosimilar have different numbers of hypoglycemic episodes compared to those on the reference analogue. The logarithm (to base e) of the follow-up time will be used as an offset variable in the model to adjust for subjects having different exposure times. The estimated treatment effect and the corresponding 95% confidence interval (CI), as well as the 2-sided p-value will be presented.

A sample SAS code fragment is provided below for reference:

```
proc genmod data = <data>;
        class trt site;
        model count = trt site / dist = negbin offset = time_log;
        lsmeans trt / ilink diff exp cl;
run;
```

All TEAEs will be listed for subjects in the Safety Analysis Set. A listing of all TEAEs leading to discontinuation of IP will be provided.

All non-treatment-emergent AEs recorded on the CRF will be listed separately for all screened subjects.

11.8.1.1 Hypoglycemic AEs based on documentation on the Hypoglycemia CRF page

Hypoglycemic AEs which are only documented on the CRF AE page and for whom the CRF Hypoglycemia page is blank or missing will not be considered in the analyses which are described below.

An additional breakdown of hypoglycemic TEAEs categorized by maximum CTCAE and ADA grade within each SOC and preferred term will be provided (Table 6, Analyses 4 - 8). The analysis will be done for hypoglycemic AEs measured with test methods "Fingerstick" and "Venous Blood Draw" (Table 6, Analyses 5 and 7). Events graded using lowest blood glucose values with test method "Other" will be presented separately (Table 6, Analyses 6 and 8). For this analysis the CTCAE and ADA grades will be derived using information documented on the Hypoglycemia page. Grading will be based on mmol/L unit (mg/dL values will be converted to mmol/L before grading).

Table 7: CTCAE grades for Hypoglycemia (based on lowest blood glucose values documented on the Hypoglycemia page)

SOC	AE Term	Grade 1	Grade 2	Grade 3	Grade 4
Metabolism and nutrition disorders	Hypoglycemia	<3.9 and ≥3.0 mmol/L	<3.0 and ≥2.2 mmol/L	<2.2 and ≥1.7 mmol/L	<1.7 mmol/L;

Table 8: ADA grades for Hypoglycemia (based on lowest blood glucose values and intervention information documented on the Hypoglycemia page)

SOC	AE Term	Grade 1	Grade 2	Grade 3
Metabolism and nutrition disorders	Hypoglycemia	<3.9 and ≥ 3.0 mmol/L	<3.0 mmol/L	A severe event characterized by altered mental and/or physical status requiring assistance selected by "Was third party intervention required for this episode of hypoglycemia?" is Yes

On the Hypoglycemia CRF page further details are documented if the answer to the question "Is this a hypoglycemic event?" on the Adverse Event CRF page is Yes. Hypoglycemic TEAEs will be reported using data recorded on both the Adverse Event page and the Hypoglycemia page as follows:

- Severe Hypoglycemia (Table 6, Analysis 9)
- Symptomatic Hypoglycemia (Table 6, Analysis 12)
- Measured Hypoglycemia (Table 6, Analysis 12)

A summary of ADA severe hypoglycemia TEAEs, symptomatic hypoglycemia TEAEs and measured hypoglycemia TEAEs will be produced, presenting the number and percentage of subjects with at least one event, as well as of the number and percentage of subjects with no events, at least one event, 1 event, 2 events, and 3 or more events (Table 6, Analysis 15). Persistent and non-persistent TEAEs will be summarized, presenting subjects with no event and at least one event (Table 6, Analysis 12).

Symptomatic or measured hypoglycemic TEAEs will be summarized by site, treatment group and overall, presenting the number of events reported, the number and percentage of subjects with at least one event (Table 6, Analysis 13). Sites with fewer than 8 subjects will be combined for summaries and analyses. A further summary by treatment group and overall will report the number and percentage of subjects with no events, at least one event, 1 event, 2 events, and 3 or more events (Table 6, Analysis 12).

All hypoglycemic events recorded on the Hypoglycemia CRF page will be listed for subjects in the SS. Additionally summary of ADA graded hypoglycemic event and TEAE by ERIPD subgroup will be produced for per protocol analysis set 2 and 3 (Table 6, Analysis 16).

11.8.2 Deaths and Serious Adverse Events

Treatment-emergent SAEs, IP-related treatment-emergent SAEs, serious hypoglycemic TEAEs (Table 6, Analysis 10), and IP-related Serious hypoglycemic TEAEs will be summarized separately by preferred term for the SS (Table 6, Analysis 11). All SAEs recorded on the CRF will be listed for subjects in the SS.

A table presenting the number and percentage of subjects by preferred term who experienced fatal TEAEs during the study will be presented for the SS. A further summary of Serious treatment-emergent SAEs by preferred term will provided. Deaths occurring in the study will also be listed for all subjects in the SS.

11.8.3 Laboratory Data

Laboratory test results will be reported in International System of Units (SI) units. For observed values below the lower limit of quantification/detection (for example total bilirubin reported as <3 µmol/L), the lower limit (3 µmol/L) will be used as the imputed value.

Laboratory values and change from baseline will be summarized using descriptive statistics by time point and treatment group. Hematology, chemistry, thyroid stimulating hormone (TSH) and free thyroxine (T4) results will be collected during screening, at visit Week 12 and visit Week 26.

Shift tables of the maximum post-baseline value will be presented by treatment group, reference range and time point. Shift tables will include all laboratory assessments. In addition, subject listings of abnormal (grade ≥ 3) post-baseline laboratory toxicities will be provided. Standard ranges from the central laboratory will be used for the laboratory analysis.

Lab assessments will be grouped for summary as follows:

- Hematology – white blood cell (WBC) parameters: WBC count and differentials
- Hematology – red blood cell (RBC) parameters: hemoglobin, hematocrit, RBC count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume
- Hematology – other parameters: platelets
- Serum chemistry – hepatobiliary parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase
- Serum chemistry – general chemistry: sodium, potassium, chloride, bicarbonate, total protein, calcium, creatine kinase, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
- Serum chemistry – renal function tests: urea, creatinine
- Thyroid – free T4, TSH

A summary assessing the potential hepatotoxicity and potential Hy's Law will be presented. A listing of these potentially hepatotoxic values (along with the corresponding amount times upper limit normal) will be presented.

A treatment-related laboratory result listing including weight, HbA1c, fasting blood glucose, and immunogenicity results will be provided. Assessments after EOT visit will be flagged in the listing.

Positive pregnancy results and dip-stick urinalysis results will be provided in a listing.

11.8.3.1 NCI CTCAE Grading

Where laboratory values are categorized into NCI CTCAE v4.03 grades, the categories are defined according to the criteria available on the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Note that grades are applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not considered. For example, Grade 4 hyperglycemia will be assigned based solely on the value of the glucose measurement, and acidosis will not be considered. Where categories are distinguished only by clinical signs or symptoms, the lowest of the possible grades will be assigned.

NCI CTCAE grades will be applied for the following lab parameters (as defined by the table in Appendix 2):

Hematology: hemoglobin (anemia), total WBC (leukopenia and leukocytosis), lymphocytes (lymphopenia), neutrophils (neutropenia), and platelets (thrombocytopenia).

Percent lymphocytes and percent neutrophils were specified in the original protocol and consequently absolute lymphocyte and neutrophil counts with corresponding normal ranges needed for the derivation of NCI CTCAE grading were not included in the central laboratory data transfers. Absolute counts for lymphocytes and neutrophils will be derived based on percent values and total WBC count as defined below only for the purpose of NCI CTCAE grading (Blumenreich, M. 1990 (9)). Calculated values will be rounded to the thousandths. NCI CTCAE grading will be derived in three steps: 1) grades 2-4 will be derived according to NCI CTCAE cutoffs, 2) if the reference range indicator for percent value indicates "LOW" and the derived absolute count is greater than 0.8 (10^9/L) for lymphocytes or 1.5 (10^9/L) for neutrophils then grade=1, and then 3) if the reference range indicator for percent value is 'NORMAL' then grade=0.

$$Absolute\ lymphocyte\ count\ (10^9/L) = (total\ WBC\ (10^9/L) * \%\ Lymphocyte)/100$$

$$Absolute\ neutrophil\ count\ (10^9/L) = (total\ WBC\ (10^9/L) * \%\ Neutrophil)/100$$

Chemistry: alkaline phosphatase, ALT, AST, bilirubin, calcium (hypocalcemia, hypercalcemia), creatinine, glucose (hyperglycemia, hypoglycemia), potassium (hyperkalemia, hypokalemia), sodium (hyponatremia, hypernatremia), and triglycerides (hypertriglyceridemia).

Laboratory measurements that are within the limits of normal and are not graded as 1-4, per the NCI CTCAE, will be coded as "Grade 0," which is defined as normal.

The maximum of the non-missing, post-randomization NCI CTCAE Grades for each of the 15 laboratory parameters (5 hematology parameters and 10 chemistry parameters (Table 6, Analysis 17 for hypoglycemia)) will be summarized using NCI CTCAE Grade in counts and percentages by treatment group using the SS.

11.8.4 Vital Signs

Values and change from baseline in vital signs will be summarized by time point and treatment group. Descriptive statistics will be shown for baseline, visit Week 2, visit Week 4, visit Week 8, visit Week 12, visit Week 16, visit Week 20 and visit Week 26. Parameters include systolic and diastolic blood pressure, and pulse.

Potentially clinically significant vital signs results will be summarized and will include the following categories:

- Pulse < 50 beats per minute
- Pulse > 120 beats per minute
- Pulse ≥ 30 beats per minute increase from baseline
- Pulse ≥ 30 beats per minute decrease from baseline
- Systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg
- Systolic blood pressure > 200 mmHg or diastolic blood pressure > 110 mmHg
- Weight ≥ 5% increase from baseline
- Weight ≥ 5% decrease from baseline

A listing of the observations with potentially clinically significant vital sign results will be provided.

11.8.5 Electrocardiograms

Values and change from baseline in ECG results will be summarized by time point and the treatment group. Descriptive statistics will be shown for baseline and visit Week 26. Potentially clinically significant ECG results will be summarized and will include the following categories:

- Heart rate < 50 beats per minute
- Heat rate > 100 beats per minute
- PR Interval ≥ 200 msec
- QRS Interval ≥ 200 msec
- QT Interval ≥ 200 msec
- QT Interval change from baseline ≥ 30 msec - < 60 msec
- QT Interval change from baseline ≥ 60 msec
- Corrected QT using Fridericia's formula (QTcF) Interval ≥ 450 - < 480 msec
- QTcF Interval ≥ 480 - < 500 msec
- QTcF Interval ≥ 500 msec
- Corrected QT using Bazett's formula (QTcB) Interval ≥ 450 - < 480 msec
- QTcB Interval ≥ 480 - < 500 msec
- QTcB Interval ≥ 500 msec

where $QTcF = QT/[(\text{heart rate}/60)^{(1/3)}]$ and $QTcB = QT/[(\text{heart rate}/60)^{(1/2)}]$.

A listing of the observations with potentially clinically significant ECG results will be provided.

12. Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

13. References

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADA	American Diabetes Association
ADaM	Analysis Data Set
AE	Adverse Event
AIA	Anti-Insulin Antibodies
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BID	Twice Daily
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standard Consortium
CGM	Continuous Glucose Monitor
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
ECG	Electrocardiogram
EIIPD	Efficacy-Interfering Important Protocol Deviation
EMA	European Medicines Agency
ERIPD	Eligibility-Related Important Protocol Deviation
EOT	End of Treatment
FAS	Full Analysis Set
FBG	Fasting Blood Glucose
FDA	Food and Drug Administration
HbA1c	Glycosylated Hemoglobin
Hgb	Hemoglobin
ICF	Informed Consent
IP	Investigational Product
ITT	Intention to Treat

IIIPD	Immunogenicity-Interfering Important Protocol Deviation
IXRS	Interactive Web Response System
LLOQ	Lower Limit of Quantification
LGH	Laboratory-Grade Hyperglycemia
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MNAR	Missing Not at Random
MWG	Mean Weighted Glucose
NAb	Anti-insulin Neutralizing Antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGSP	National Glycohemoglobin Standardization Program
OAM	Other Antidiabetes Medication
OSADD	Overall Subject Average Daily Dose
PPS	Per Protocol Analysis Set
QD	Daily
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SI	International System of Units
SOC	System Organ Class
SS	Safety Analysis Set
T4	Free Thyroxine
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, and Listings
TOST	Two One-Sided Tests

TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell

Appendix 2 NCI CTCAE v 4.03 Grading for Laboratory Values and QTc

SOC	AE Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	White blood cell decreased (Leukopenia)	<LLN - 3000/mm^3; <LLN - 3.0 × 10^9/L	<3000 - 2000/mm^3; <3.0 - 2.0 × 10^9/L	<2000 - 1000/mm^3; <2.0 - 1.0 × 10^9/L	<1000/mm^3; <1.0 × 10^9/L
Investigations	White blood cell increased (Leukocytosis)	-	-	>100,000/mm^3	-
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Investigations	Lymphocyte count decreased (Lymphopenia)	<LLN - 800/mm^3; <LLN - 0.8 x10^9/L	<800 - 500/mm^3; <0.8 - 0.5 × 10^9/L	<500 - 200/mm^3; <0.5 - 0.2 × 10^9/L	<200/mm^3; <0.2 × 10^9/L
Investigations	Neutrophil count decreased (Neutropenia)	<LLN - 1500/mm^3; <LLN - 1.5 × 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 × 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 × 10^9/L	<500/mm^3; <0.5 × 10^9/L
Investigations	Platelet count decreased (Thrombocytopenia)	<LLN - 75,000/mm^3; <LLN - 75.0 × 10^9/L	<75,000 - 50,000/mm^3; <75.0 - 50.0 × 10^9/L	<50,000 - 25,000/mm^3; <50.0 - 25.0 × 10^9/L	<25,000/mm^3; <25.0 × 10^9/L
Investigations	Alkaline phosphatase increased	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Alanine aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Aspartate aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN

Investigations	Blood bilirubin increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 -1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life threatening consequences
Investigations	Creatinine increased	>1 - 1.5 × baseline; >ULN - 1.5 × ULN	>1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	>3.0 × baseline; >3.0 - 6.0 × ULN	>6.0 × ULN
Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Metabolism and nutrition disorders	Hyperkalemia	Blood potassium value >ULN - 5.5 mmol/L	Blood potassium value >5.5 - 6.0 mmol/L	Blood potassium value >6.0 - 7.0 mmol/L; hospitalization indicated	Blood potassium value >7.0 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypokalemia	Blood potassium value <LLN - 3.0 mmol/L	Blood potassium value <LLN - 3.0 mmol/L; symptomatic; intervention indicated	Blood potassium value <3.0 - 2.5 mmol/L; hospitalization indicated	Blood potassium value <2.5 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyponatremia	Plasma sodium <LLN - 130 mmol/L	-	Plasma sodium <130 - 120 mmol/L	Plasma sodium <120 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypernatremia	Plasma sodium >ULN - 150 mmol/L	Plasma sodium >150 - 155 mmol/L	Plasma sodium >155 - 160 mmol/L; hospitalization indicated	Plasma sodium >160 mmol/L; life-threatening consequences

Metabolism and nutrition disorders	Hypertriglyceridemia	Serum triglycerids 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Serum triglycerids >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Serum triglycerids >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Serum triglycerids >1000 mg/dL; >11.4 mmol/L; life-threatening consequences
Investigations	Electrocardiogram QT corrected interval prolonged	QTc 450-480 ms	QTc 481-500 ms	QTc ≥ 501 ms on at least 2 separate ECGs	QTc ≥ 501 ms or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; Hgb = hemoglobin; LLN = lower limit of normal; QTc = corrected QT interval; SOC = system organ class; ULN = upper limit of normal;

Note: Laboratory measurements that are within the institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0" which is defined as normal.

Appendix 3 Tables, Figures, Listings, and Supportive SAS Output Appendices

The TFL shells for this study are provided in a separate document titled "Gan & Lee GL-GLAT2-3002 TFL Shells Version 3.0.docm," which includes a complete table of contents listing all required outputs.

Appendix 4 Immunogenic- and Efficacy-Interfering Important Protocol Deviations

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
1. INCLUSION CRITERIA	**Any deviation from inclusion criteria after the ICF has been signed**				
1. INCLUSION CRITERIA n. 1	Enrollment of a male or a nonpregnant, nonlactating female not between the ages of 18 and 75 years, inclusive.	Yes	1	No	No
1. INCLUSION CRITERIA n. 2	Enrollment of a subject unable to provide written, personally signed, and dated informed consent before initiating any study-related procedures.	Yes	2	No	No
1. INCLUSION CRITERIA n. 3	Enrollment of a subject unable to understand and fully comply with all study procedures and restrictions.	Yes	3	No	No
1. INCLUSION CRITERIA n. 4	Enrollment of a subject, insulin-naïve, with a confirmed diagnosis of type 2 diabetes mellitus who has not been on at least 2 approved OAMs for at least 12 weeks before screening.	Yes	4.1	Yes	Yes
1. INCLUSION CRITERIA n. 4	Enrollment of a subject, who is treated with a basal insulin, with a confirmed diagnosis of type 2 diabetes mellitus who has not been treated with insulin for at least 6 months or has not been on at least 1 approved OAM or the type or brand of insulin has changed within 6 months prior to screening.	Yes	4.2	Yes	Yes
1. INCLUSION CRITERIA n. 5	Enrollment of an insulin-naïve subject with HbA1c > 11.0%.	Yes	5.1	No	Yes
1. INCLUSION CRITERIA n. 5	Enrollment of a subject previously on a basal insulin regimen with HbA1c < 7.0% or > 11.0%.	Yes	5.2	No	Yes
1. INCLUSION CRITERIA n. 6	Enrollment of subjects with body mass index (BMI) < 19 kg/m2 or > 35 kg/m2.	Yes	6	Yes	Yes
1. INCLUSION CRITERIA n. 7	Enrollment of a subject unable to adhere to a prudent diet and exercise regimen recommended by the medical provider, and not willing to maintain these consistently for the duration of the study.	Yes	7	Yes	Yes
1. INCLUSION CRITERIA n. 8	Enrollment of a subject who had taken concomitant thyroid medications without having a stable dosage for 90 days before screening.	Yes	8	Yes	Yes

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
2. EXCLUSION CRITERIA	**Any deviation from exclusion criteria after the ICF has been signed**	Yes			
2. EXCLUSION CRITERIA n. 1	Enrollment of a subject who participated in another clinical study or use of any study drug within 30 days before screening.	Yes	1	Yes	Yes
2. EXCLUSION CRITERIA n. 2	Enrollment of subject with previous use of a biosimilar insulin, either basal or bolus.	Yes	2	Yes	Yes
2. EXCLUSION CRITERIA n. 3	Enrollment of subject with diabetic ketoacidosis within a year before screening.	Yes	3	No	No
2. EXCLUSION CRITERIA n. 4	Enrollment of a subject with a history of brittle type 2 diabetes mellitus within the year before screening (e.g., multiple hospitalizations related to diabetes mellitus and/or severe hypoglycemia for which the subject required 3rd party assistance).	Yes	4	Yes	Yes
2. EXCLUSION CRITERIA n. 5	Enrollment of a subject with any severe, delayed sequela of diabetes mellitus, e.g., worsening end-stage renal disease, advanced coronary artery disease, or myocardial infarction within the year before screening, or autonomic peristaltic problems, e.g., gastroparesis.	Yes	5	Yes	Yes
2. EXCLUSION CRITERIA n. 6	Enrollment of a subject with anticipated change in insulin used during the study.	Yes	6	Yes	Yes
2. EXCLUSION CRITERIA n. 7	Enrollment of a subject without obtaining TSH and T4 results before randomization and both TSH and T4 results are within normal ranges measured by the central laboratory after randomization (during the treatment period).	Yes	7.1	No	No
2. EXCLUSION CRITERIA n. 7	Enrollment of a subject without obtaining TSH and T4 results before randomization and TSH and/or T4 results are not available or out of normal ranges after randomization (during the treatment period).	Yes	7.2	Yes	Yes
2. EXCLUSION CRITERIA n. 8	Enrollment of a subject with BMI < 19 kg/m2 or > 35 kg/m2.	Yes	8	Yes	Yes
2. EXCLUSION CRITERIA n. 9	Enrollment of a subject without obtaining hematology or chemistry tests or any clinically significant (in the opinion of the Investigator) hematology or chemistry test results at	Yes	9	Yes	Yes

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
	screening, including any liver function test > 3 × the upper limit of normal.				
2. EXCLUSION CRITERIA n. 10	Enrollment of a subject with documented anti-insulin antibodies in the past.	Yes	10	Yes	Yes
2. EXCLUSION CRITERIA n. 11	Enrollment of a subject treated with glucocorticosteroids (newly prescribed or high dose), immunosuppressants, or cytostatic agents within 60 days before screening; or treated with a prohibited medication up to randomization.	Yes	11	Yes	Yes
2. EXCLUSION CRITERIA n. 12	Enrollment of a subject using medication intended to cause weight loss or weight gain during the screening.	Yes	12	Yes	Yes
2. EXCLUSION CRITERIA n. 13	Enrollment of a subject with a history of alcohol or substance use disorder within the 2 years before screening.	Yes	13	No	No
2. EXCLUSION CRITERIA n. 14	Enrollment of a subject with any history of previous or anticipated treatment with interferons.	Yes	14	Yes	Yes
2. EXCLUSION CRITERIA n. 15	Enrollment of a subject with any history of malignant disease within 5 years before screening, except for adequately treated basal cell carcinoma.	Yes	15	Yes	Yes
2. EXCLUSION CRITERIA n. 16	Enrollment of a subject with a severe concomitant physical or psychiatric diseases or conditions.	Yes	16	No	No
2. EXCLUSION CRITERIA n. 17	Enrollment of a subject with a history of a positive test result for HIV, hepatitis B, or hepatitis C.	Yes	17	Yes	Yes
2. EXCLUSION CRITERIA n. 18	Enrollment of a subject with any history of pancreatitis or pancreatectomy.	Yes	18	Yes	Yes
2. EXCLUSION CRITERIA n. 19	Enrollment of a subject with any diagnosis or condition that requires the subject to undergo procedures that could decrease antibodies in plasma or that would require treatment with immunosuppressant agents.	Yes	19	Yes	Yes
2. EXCLUSION CRITERIA n. 20	Enrollment of a subject with any condition e.g., splenectomy, autoimmune disease, or rheumatologic disease, that could affect immunologic responses, could indicate an altered immune system, or could require	Yes	20	Yes	Yes

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
	treatment with a prohibited concomitant medication.				
2. EXCLUSION CRITERIA n. 21	Enrollment of a subject with any unresolved infection or a history of active infection within 30 days before screening other than mild or viral illness (as judged by the Investigator).	Yes	21	Yes	Yes
2. EXCLUSION CRITERIA n. 22	Enrollment of a subject with any disease or condition that in the opinion of the Investigator could confound the study results or limit the subject's ability to participate in the study or comply with follow-up procedures; or any other factor that would indicate a significant risk of loss to follow up.	Yes	22	Yes	Yes
2. EXCLUSION CRITERIA n. 23	Enrollment of a subject with intolerance or history of hypersensitivity to insulin glargine or any excipient of IP.	Yes	23	Yes	Yes
2. EXCLUSION CRITERIA n. 24	Enrollment of a subject unable or unwilling to wear the CGM sensor as required for the study, or to comply with the concomitant medication requirements in the FreeStyle Libre Pro Indications and Important Safety Information, during the CGM periods.	Yes	24	No	No
3. STUDY DRUG	**Deviations related to study drug**				
3. STUDY DRUG	A single dose of study drug is not administered by the subject due to reason(s) other than safety in any given 2-week span during treatment period.	No	1	No	No
3. STUDY DRUG	More than one dose of study drug is not administered by the subject due to reason(s) other than safety in any given 2-week span during treatment period.	Yes	2	No	Yes
3. STUDY DRUG	Subject received the study drug that was assigned to another subject, which is consistent with their assigned treatment.	No	3	No	No
3. STUDY DRUG	Subject received the study drug that was assigned to another subject, which is different than their assigned treatment.	Yes	4	Yes	Yes
3. STUDY DRUG	Subject failed to return the study drug.	No	5	No	No

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
3. STUDY DRUG	Failure to adjust doses of the study drug according to the instructions provided by the Investigator (especially where doses are expected to have a major impact on outcome) during the treatment period or failure to adjust the previously prescribed basal insulin during the Dose Optimization period.	Yes	6	No	Yes
3. STUDY DRUG	BID dosing of the study drug.	No	7	No	No
3. STUDY DRUG	GCP compliance - Drug Accountability not properly documented by site staff.	No	8	No	No
3. STUDY DRUG	A temperature excursion occurred and the proper notification, quarantine and release processes were not followed. The study drug in question was not administered to subjects.	No	9	No	No
3. STUDY DRUG	A temperature excursion occurred and the proper notification, quarantine and release processes were not followed. The study drug in question was administered to subjects without documentation of its stability.	Yes	10	Yes	Yes
3. STUDY DRUG	Mishandling, potential theft, loss of study drug at the site.	No	11	No	No
3. STUDY DRUG	Consistent or repeated failure by subject to document drug administration in the Mealtime and Insulin Dose Record Card during the CGM wearing period.	No	12	No	No
3. STUDY DRUG	Any deviation not covered by current Protocol Deviation Guidance codes related to the study drug.	TBD	13	TBD	TBD
4. ASSESSMENT - SAFETY	**Failure to complete any safety assessments at study visits.**				
4. ASSESSMENT - SAFETY	Protocol-defined baseline evaluations not performed before institution of the study drug.	Yes	1	No	No
4. ASSESSMENT - SAFETY	Failure to take action in response to apparent Hypoglycemia and failure to appropriately monitor the subject.	Yes	2	No	No
4. ASSESSMENT - SAFETY	Failure to report Serious Adverse Event (SAE) to the IRB/IEC or Sponsor within 24 hrs of knowledge of event.	Yes	3	No	No
4. ASSESSMENT - SAFETY	A failure to complete a single or multiple safety assessments (urinalysis, pregnancy test, vital signs, body weight) at two consecutive visits.	Yes	4	No	No

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
4. ASSESSMENT - SAFETY	A failure to complete a single safety assessment (hematology, chemistry, thyroid labs, urinalysis, pregnancy test, vital signs, body weight) at a single visit.	No	5	No	No
4. ASSESSMENT - SAFETY	Performing additional study procedures (not listed in the protocol schedule of procedures and assessments except for unscheduled visits done for safety reasons) without approval of Sponsor and IRB/EC.	Yes	6	No	No
4. ASSESSMENT - SAFETY	Failure to complete single or multiple safety assessments (hematology, chemistry, thyroid labs, urinalysis, pregnancy test, vital signs, body weight, ECG, PE) at the final or Early Termination (ET) visit.	Yes	7	No	No
4. ASSESSMENT - SAFETY	AEs not assessed at a study visit (excluding hypoglycemia and not clinically significant hyperglycemia).	Yes	8	No	No
4. ASSESSMENT - SAFETY	Subject becomes pregnant during the study and is not withdrawn from the study.	Yes	9	No	No
4. ASSESSMENT - SAFETY	Partner of a male subject becomes pregnant during the study and pregnancy not reported.	Yes	10	No	No
4. ASSESSMENT - SAFETY	Failure to repeat laboratory tests for unexplained abnormal laboratory test results.	No	11	No	No
4. ASSESSMENT - SAFETY	A failure to complete multiple safety assessments (hematology, chemistry, thyroid labs, urinalysis, pregnancy test, vital signs, body weight) at a single visit.	Yes	12	No	No
4. ASSESSMENT - SAFETY	Failure to complete urine pregnancy test for all women of childbearing potential at study visit(s) and confirmed pregnancy later.	Yes	13	No	No
4. Assessment - Safety	Failure to follow the protocol (or any safety related plans) such that the safety of the subject or other subjects in the study is significantly impacted.	Yes	14	No	No
5. ASSESSMENT - EFFICACY	**Failure to complete any efficacy assessments at study visits.**				
5. ASSESSMENT - EFFICACY	Failure to complete HbA1c and/or Fasting Blood Glucose sampling at two consecutive visits, or at Baseline (Screening or Day 1), or at V9/Early Termination.	Yes	1	No	Yes
5. ASSESSMENT - EFFICACY	Failure to complete HbA1c and/or Fasting Blood Glucose sampling at a visit other than at	No	2	No	No

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
	Baseline (Screening or Day 1), or at V9/Early Termination.				
6. VISIT WINDOW	**Whole visit missed or out of visit window.**				
6. VISIT WINDOW	Missing an entire visit	No	1	No	No
6. VISIT WINDOW	Visit or procedure out of window	No	2	No	No
7. INFORMED CONSENT (ICF)	**ICF process not conducted per ICH/GCP Guidelines or CFR.**				
7. INFORMED CONSENT (ICF)	Subject signed a version of the ICF that is not approved by IRB/IEC.	Yes	1	No	No
7. INFORMED CONSENT (ICF)	Failure to obtain informed consent (or amended ICF), or Informed consent (or amended ICF) obtained after initiation of study procedures. Either missing subject signatures or missing designated caregiver's signatures (if subject cannot sign) on the consent form.	Yes	2	No	No
7. INFORMED CONSENT (ICF)	Missing original signed and dated consent form (only a photocopy available) or inappropriate documentation of informed consent, such as missing signatures (other than the subject's or designated caregiver's).	Yes	3	No	No
7. INFORMED CONSENT (ICF)	Use of an invalid, or outdated consent form.	Yes	4	No	No
7. INFORMED CONSENT (ICF)	Inadequate documentation of the informed consent process in subject source documents.	Yes	5	No	No
8. SAMPLE MANAGEMENT - HbA1c	**Site does not manage the HbA1c sample per laboratory manual**				
8. SAMPLE MANAGEMENT - HbA1c	HbA1c sample not managed according to Laboratory Manual (e.g. shipment timelines are not followed however sample storage and stability of the sample are not impacted).	No	1	No	No
9. SAMPLE MANAGEMENT - AIA/NAB	**Site does not manage the AIA/NAB sample per protocol and/or pre laboratory manual**				
9. SAMPLE MANAGEMENT - AIA/NAB	Any AIA/NAB samples not collected at protocol defined visits.	Yes	1	No	No
9. SAMPLE MANAGEMENT - AIA/NAB	Any AIA/NAB samples not collected pre-dose during the protocol defined visits.	No	2	No	No
9. SAMPLE MANAGEMENT - AIA/NAB	Any AIA/NAB samples not managed according to Laboratory Manual (e.g. shipment timelines are not followed however, sample storage and stability of the samples are not impacted).	No	3	No	No
9. SAMPLE MANAGEMENT - AIA/NAB	Storage temperature of AIA/NAB samples not managed according to Laboratory Manual.	Yes	4	Yes	No

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
10. PROHIBITED CON-MEDS	**Use of prohibited Concomitant-Medication (Con-Meds)**				
10. PROHIBITED CON-MEDS	Received a prohibited concomitant medication according to protocol after randomization (during the treatment period).	Yes	1	Yes	Yes
11. Continuous Glucose Monitor (CGM) DEVICE	**Continuous Glucose Monitor (CGM) issues**				
11. CGM DEVICE	Repeated or consistent failure of the subject to return the CGM device.	No	1	No	No
11. CGM DEVICE	Repeat or persistent failure of the subject to complete and return the 8-day Mealtime & Insulin Dose Record.	No	2	No	No
11. CGM DEVICE	Failure by the site to apply the CGM sensor at the appropriate study timepoint.	No	3	No	No
12. UNDOCUMENTED HYPOGLYCEMIC EVENT RECORD	**Hypoglycemic Event reporting issue**				
12. UNDOCUMENTED HYPOGLYCEMIC EVENT RECORD	Failure to report a hypoglycemic event.	Yes	1	No	No
12. UNDOCUMENTED HYPOGLYCEMIC EVENT RECORD	Hypoglycemic event reported, but not in a timely manner.	No	2	No	No
13. OTHER	**Others Not Included in the above mentioned categories**				
13. OTHER	Failure to comply with requirements of the IRB for documentation and necessary notification.	Yes	1	No	No
13. OTHER	Any deviation not covered by current Protocol Deviation Guidance codes.	TBD	2	No	No
13. OTHER	The number of subjects enrolled by a site is over a pre-approved site enrollment limit without permission.	No	3	No	No
13. OTHER	Subject not registered in IXRS prior to initiation of the study treatment.	Yes	4	No	No
13. OTHER	Any repeated inconsistency of source documents and eCRF (e.g. Date of birth, etc.).	Yes	5	No	No
13. OTHER	Amended ICF signed at a later visit but no new procedures as per the amended Protocol were implemented before the signature.	No	6	No	No