Statistical Analysis Plan

Sponsor:	Gan & Lee Pharmaceuticals USA Corporation
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PRA Project Id:	GNLT1DMG-T1DMGL
Version Date:	27-May-2021
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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 1 diabetes mellitus
CRF Version No./Date:	5.0/14-Feb-2020

Approvals

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Change History

Version/Date	Change Log
1.0 / 26-Apr-2019	Final (stable) version
2.0 / 22-Oct-2020	Specified sample size and power calculation Extended the section Definitions for ERIPD, average daily dose, overdose, TEAE Updated the definition of safety analysis set
3.0 / 27-May-2021	Specified changes from Protocol Updated the definition of TEAE Added sections Site Closure Related Database limitations and Randomization Stratification and Analysis Covariate Updated Table 6 describing hypoglycemic events summaries and analyses Restructuring of Section 11.8.2 describing Hypoglycemic TEAEs

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 of HbA1c at visit Week 26 from baseline between the two treatment arms. Although efficacy is not specified in the protocol objectives as a key objective, evaluation of the efficacy measured by HbA1c at visit Week 26 of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus® is considered a key secondary endpoint of the study.
- To evaluate the percentage of subjects who achieve a fasting blood glucose (FBG) test result of ≤ 6.0 mmol/L (≤ 108.0 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

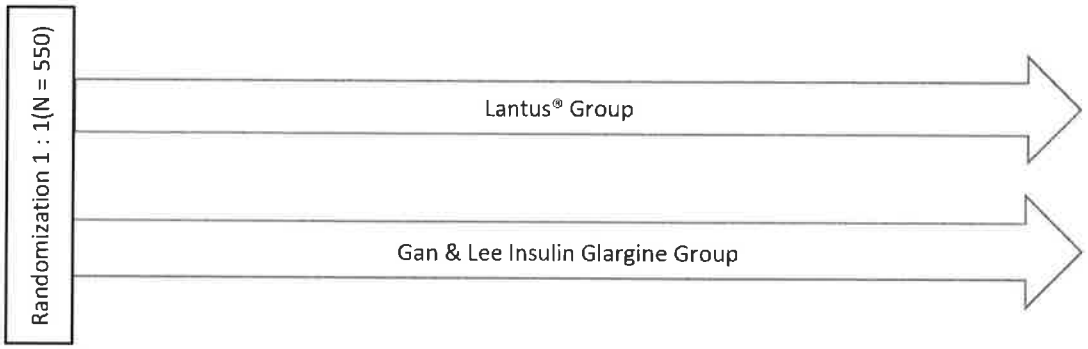
- To investigate the retrospective hypoglycemic rate and time in hypoglycemia and hyperglycemia using continuous glucose monitoring (CGM) data
- To examine the relationship between the plasma concentrations of insulin glargine, M1, and M2, and immunogenic response

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 1 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 and randomly assigned in a 1:1 allocation ratio to receive

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; DA = Basal insulin dose optimization; 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.

5.1 Sample Size and Power

Enrollment was planned for 550 subjects overall (275 subjects per treatment group). The primary analysis for the 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) 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 the 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 total 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% (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 had 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 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.

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 subject regardless 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 ≤ 6.0 mmol/L (≤ 108.0 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 hypoglycemia rate
- Time in hypoglycemia and hyperglycemia event based on CGM data
- Relationship between plasma concentrations of insulin glargine, M1, and M2, and AIA titers

8) Diabetes Disease Duration

The duration of diabetes is defined as the number of years from the date of original diagnosis of Type 1 Diabetes Mellitus to the date of randomization (presented in full years):

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

If the date of Type1 Diabetes Mellitus diagnosis 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) QD Compliance Dosing Regimen

QD Compliance is 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. If a subject does not answer Yes then they are marked as No in all associated outputs.

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 or Other category with deviation that has description "Inadequate source documentation that is required to support eligibility assessment". Site POL008 has been placed in this Other category and is used in this derivation as the deviation relates to documentation of eligibility. (refer to Appendix 4 Immunogenic- and Efficacy-Interfering Important Protocol Deviations for details).

12) End of Treatment visit

The End of Treatment visit (EOT) is defined as the scheduled visit labelled in data as 'Visit 9 Week 26/ End of Study'. This includes any subject who discontinues from treatment before visit Week 26 who has scheduled Visit 9 procedures performed at a 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.

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 (study day 182 +/- 3 days as per protocol) 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

- 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.

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 11.8.2.1).

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 Medical Dictionary for Regulatory Activities (MedDRA) High Level Term = "Injection site reaction".

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 IP-related.

6) 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.

7) 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.

8) Treatment-emergent adverse events

Treatment-emergent adverse event (TEAE) is an event that started or worsened in severity on or after the day of the first dose of IP but not more than 30 days after the subject's last dose of IP.

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.

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 assignment was randomized, 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.

8.4 PK Analysis Set

According to protocol Amendment 3, the Pharmacokinetic (PK) Analysis Set comprises all randomized subjects who receive at least 1 partial dose and provide at least 1 pre-dose assessment at any study visit that is sufficient to derive plasma concentration of insulin glargine, M1, or M2. Subjects in the PK analysis set will be grouped according to treatment they actually received (defined in Section 7.1).

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), and will be 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.
- Arcinova: PK data
- 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.

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 country
- Number and percentage of subjects who completed the comparative portion (Visits 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 treatment discontinuation (also as a Kaplan-Meier plot)
- Number and percentages of subjects completed the study, and reasons for discontinuation collected on the CRF End of study page will be summarized for the FAS, SS, and the PPS.

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.

A listing of subjects' randomization numbers, 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 will be finalized before the database lock.

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 Immunogenic- and Efficacy-Interfering Important Protocol Deviations 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 also 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.

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 country-adjusted difference in proportions 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 is the country-adjusted 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. The visit window (defined in Section 7.1) will only be limited to include assessment within 210 days from the first dose.

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 adjusted by country (CNTRY) estimating the country-adjusted difference in proportions along with the corresponding 90% confidence interval (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:

Category	Sample Availability	Imputation	Likely Scenarios
		• Subject will be counted as 'NOT developing a treatment-induced AIA' if both Week 12 and Week 26 results are negative.	
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.

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 newly 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 country-adjusted logistic regression 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 country-adjusted logistic regression 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
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

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 upper limit of visit window defined in Section 7.1 (that is, for study day <= 210).

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 and stratification factor of country (CNTRY) included as fixed effects 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. Limits of the imputed value will use the minimum of HbA1c values and the maximum of all HbA1c values assessed, and rounded to the nearest integer. These values are found in the database to be minimum as 5 and the maximum as 13. 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 MI analyzed using ANCOVA with treatment and stratification factor of country (CNTRY) included as fixed effects 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 subjects 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 Insulin Glargine Injection and Lantus® will be considered non-inferior if the 95% CI is below the margins of 0.4 and 0.3%, respectively.

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 visit 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, country, 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)

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= 337850 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 Endpoints

11.7.2.1 Proportion of Subjects Achieving Glycemic Control

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

- The number and percentage of subjects who achieve an FBG test result of ≤ 6.0 mmol/L (≤ 108.0 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. Subjects without values available at week 26 will be considered as having not achieved glycemic control. Samples from subjects who have discontinued study but returned to provide assessment for Week 26 will be included for this analysis.

Additionally, number and percentages of subjects who achieve an FBG test result of ≤ 6.0 mmol/L (≤ 108.0 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

Table 6: Listing of hypoglycemic event summaries and analyses

Analysis description	Section Reference	Tables Associated
1. Summary of Retrospective Continuous Glucometer Monitor (CGM): Hypoglycemia Rate	Section 11.7.3.1	Table 14.3.3.4.1
2. Retrospective Analysis of Continuous Glucometer Monitoring (CGM): Time in Hypoglycemia, Hyperglycemia and Euglycemia	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. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term	Section 11.8.1	Table 14.3.2.2
5. 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)	Section 11.8.2.1	Table 14.3.2.6.1
6. Severe Hypoglycemic Treatment-Emergent Adverse Events by Preferred Term	Section 11.8.1	Table 14.3.2.7
7. Serious Hypoglycemic Adverse Events by Preferred Term	Section 11.8.3	Table 14.3.2.13
8. IP-Related Serious Hypoglycemic Adverse Events by Preferred Term	Section 11.8.3	Table 14.3.2.14
9. Summary of Symptomatic or Persistent Hypoglycemic Treatment-Emergent Adverse Events	Section 11.8.2	Table 14.3.2.17
10. Summary of Symptomatic or Persistent Hypoglycemic Treatment-Emergent Adverse Events by Site	Section 11.8.2	Table 14.3.2.18
11. Analysis of Hypoglycemic Treatment-Emergent Adverse Events	Section 11.8.2	Table 14.3.2.19
12. Summary of Reported ADA Hypoglycemic Treatment-Emergent Adverse Events	Section 11.8.2.2	Table 14.3.2.20
13. Overall Summary and Analysis of Treatment-Emergent Adverse Events by ERIPD Subgroup in SS, PPS2, and PPS3	Section 11.8.1	Table 14.3.2.21; 14.3.2.22; 14.3.2.23; 14.3.2.24
14. Maximum Post-baseline Fasting Glucose CTCAE Grade	Section 11.8.4.1	Table 14.3.3.4.16

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

- CTCAE Grade ≥ 3 TEAEs
- Hypoglycemic TEAEs
- CTCAE Grade 3 or Greater Hypoglycemic AEs
- IP-related TEAEs
- CTCAE Grade ≥ 3 IP-related TEAEs
- Fatal AEs
- SAEs
- IP-related SAEs
- Serious Hypoglycemic AEs
- IP-related Serious Hypoglycemic AEs
- AEs Pertaining to 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 hypoglycemic event rate will be compared between treatment groups using a negative binomial regression model (Table 6, Analysis 11). The response variable in the model will be the number of hypoglycemia events. The model will include factors for treatment group and site. Site has been included as a factor as different handling of documentation of hypoglycemia event are identified. 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% 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 SS. 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.

11.8.2 Hypoglycemic Treatment Emergent Adverse Events

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

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

- Severe Hypoglycemic event (Table 6, Analysis 6)
- Symptomatic Hypoglycemic event (Table 6, Analysis 9)

nutrition disorders				"Was third party intervention required for this episode of hypoglycemia?" is Yes

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 12).

11.8.3 Deaths and Serious Adverse Events

SAEs, IP-related SAEs, serious hypoglycemic (Table 6, Analysis 7), and IP-related Serious hypoglycemic events will be summarized separately by preferred term for the SS (Table 6, Analysis 8). 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 be provided. Deaths occurring in the study will also be listed for all subjects in the SS.

11.8.4 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 – 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.

Post-baseline potentially clinically significant (PCS) 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 PCS vital sign results will be provided.

11.8.6 Electrocardiograms

Values and change from baseline in ECG results will be summarized by time point and treatment group. Descriptive statistics will be shown for baseline and visit Week 26. Post-baseline PCS 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 ≥ 120 msec
- QT Interval ≥ 450 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 PCS 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.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADA	American Diabetes Association
ADaM	Analysis Data Model
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

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

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	Fasting glucose value <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	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypokalemia	Blood potassium value <LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyponatremia	Plasma sodium <LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypernatremia	Plasma sodium >ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences

Appendix 3 Shells of Tables, Figures, Listings

The TFL shells for this study are provided in a separate document titled "Gan & Lee GL-GLAT1-3001 TFL Shells Version 3.0_updated_annotated.docm," which includes a complete table of contents listing all required outputs.

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
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 1 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/m^2 or > 35 kg/m^2.	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 screening, including any liver function test > 3 × the upper limit of normal.	Yes	9	Yes	Yes
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

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
	follow-up procedures; or any other factor that would indicate a significant risk of loss to follow up.				
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 / INVESTIGATIONAL PRODUCT (IP)	**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
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	No	9	No	No

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
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 Baseline (Screening or Day 1), or at V9/Early Termination.	No	2	No	No
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.**				

Type of Deviation/ Code	Deviation Description	Important protocol deviation	Sub-Category	PD Effect on Immunogenicity	PD Effect on Efficacy
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
13. OTHER	Inadequate source documentation that is required to support eligibility assessment.	Yes	7	No	No

Data Point	Subject	Folder	CRF	Log Line Number in EDC	Issue	Reason discrepancy is irreconcilable
10	1USA014005	Visit 4	Laboratory Data - Central Processing 3	1	Fasting Blood Glucose collection time was 08:20, and result was clinically significant. However, corresponding AE17 HYPOGLYCEMIA had the start time 08:50. Unable to query as the site was closed.	Site closure
11	1USA014006	Adverse Events	Adverse Events	12	AE#12 was not recorded as indication in CM#3 IBUPROFEN. Unable to query as the site was closed.	Site closure
12	1USA023002	Concomitant Medications	Prior/Concomitant Medication	8	Needed to update indication "TO TREAT HYPOGLYCEMIA" to "Prophylaxis for hypoglycemia". Query was issued but cancelled due to site closure.	Site closure
13	1USA023003	Adverse Events	Adverse Events	134	Needed to clarify if the Action Taken with Study Treatment should be 'Dose Interrupted'. Query was issued but cancelled due to site closure.	Site closure
14	1USA023003	Adverse Events	Adverse Events	135	Needed to clarify if the Action Taken with Study Treatment should be 'Dose Interrupted'. Query was issued but cancelled due to site closure.	Site closure
15	1USA023003	Adverse Events	Adverse Events	135	Needed to confirm if the hospital-provided Lantus and Humalog were given in the hospital during this time. If so, then Con Med Log should be updated to include. Query was issued but cancelled due to site closure.	Site closure
16	1USA023003	Adverse Events	Adverse Events	134	Needed to confirm if the hospital-provided Lantus and Humalog were given in the hospital during this time. If so, then Con Med Log should be updated to include. Query was issued but cancelled due to site closure.	Site closure
17	1USA023003	Concomitant Medications	Prior/Concomitant Medication	10	The SAE report indicates that Heparin was also given for the event on 01Aug18. Needed to clarify if it should be added to the Concomitant Medications page. Query was issued but cancelled due to site closure.	Site closure
18	1USA023009	Adverse Events	Adverse Events	6	For AE#6 GANGRENE, the drug was withdrawn due to 3 SAEs. Needed to query to clarify which SAE was responsible. And per the PD the subject was on his father's medication from 11-17Aug yet the last dose of study drug was 16Aug. And the AE says the drug was withdrawn due to SAE(s) yet the End of Study page reason for DC is Withdrawal of consent. Also, there is drug accountability recorded up to 07Sep. Unable to query as the site was closed.	Site closure
19	1USA023009	Adverse Events	Adverse Events	1	During the SAE event the subject was reported as having blood glucose values 'in the 600's' on admission. Needed to clarify if the blood glucose values were clinically significant. Query was issued but cancelled due to site closure.	Site closure
20	1USA023009	Concomitant Medications	Prior/Concomitant Medication	1	Based on SAE report, Novolog was taken by this subject, however it was not recorded on the Con Med Log. Query was issued but cancelled due to site closure.	Site closure
21	1USA023010	Common Forms	Drug Accountability	N/A	The estimated # expected pens based on average doses was 26, but total pens on IP recon log was 25 and total pens lost, damaged or used per IRT was 21. Unable to query as the site was closed.	Site closure

Data Point	Subject	Folder	CRF	Log Line Number in EDC	Issue	Reason discrepancy is irreconcilable
34	1USA066005	Common Forms	Drug Accountability	3	Drug Accountability showed that 0 were returned, but no return date. Per previous query, it appears drug was not returned. Should have requeried that if subject did not return any drug, then date returned and # returned should be blank. Unable to query as the site was closed.	Site closure
35	1USA066005	Common Forms	Drug Accountability	4	Drug Accountability showed that 0 were returned, but no return date. Per previous query, it appears drug was not returned. Should have requeried that if subject did not return any drug, then date returned and # returned should be blank. Unable to query as the site was closed.	Site closure
36	1USA066005	Telephone Contact Week 6	Average Daily Dose of Study Drug	N/A	The average daily dose recorded at TC Week 6 (16U) was significantly higher than average dose recorded at Visit 3 Week 2 (8U). Unable to query as the site was closed.	Site closure
37	1USA066005	Visit 4	Average Daily Dose of Study Drug	N/A	The average daily dose recorded at Visit 4 (16U) was significantly higher than average dose recorded at Visit 3 Week 2 (8U). Unable to query as the site was closed.	Site closure
38	1USA066006	Adverse Events	Adverse Events	1	Query should have been issued to complete the other seriousness criteria which were left blank, because this was a serious adverse event and all criteria should have been answered. Unable to query as the site was closed.	Site closure
39	1USA066006	Adverse Events	Adverse Events	1	For AE#4, Start date, end date, and ongoing were missing. Site was queried and responded that all are unknown. Site response, "All information on AE is unknown as subject mentioned to SC, but didnt bring a log and no other information was provided. SC no longer working at site."	Site closure
40	1USA066006	Visit 1	Medical History	N/A	Query was issued: "Safety Database Query: Hyperlipidemia, Acute kidney injury and GERD, present in safety database, however missing in EDC, please kindly confirm the associated MHs or add accordingly in EDC." Site responded "correct" but did not add these conditions to the MH or clarify if they didn't apply. Unable to requery as the site was closed.	Site closure
41	1DEU006004	Concomitant Medications (1)	Prior/Concomitant Medications	5	The following fields contain new or updated data but have not been SDV'd/Re-SDV'd: Indication, What was the ID for the adverse event(s) for which the medication was taken? This issue was added to the irreconcilable log because new or changed data cannot be SDV (the site cannot do remote SDV). This was discussed with clinical and with the sponsor on 26May21.	Site unable to complete rSDV
42	1DEU006007	Adverse Events (1)	Adverse Events	1	The following fields contain new or updated data but have not been SDV'd/Re-SDV'd: Is the adverse event a medically important event not covered by other "serious" criteria This issue was added to the irreconcilable log because new or changed data cannot be SDV (the site cannot do remote SDV). This was discussed with clinical and with the sponsor on 26May21.	Site unable to complete rSDV
43	1DEU006007	Concomitant Medications (1)	Prior/Concomitant Medications	10	The following fields contain new or updated data but have not been SDV'd/Re-SDV'd: What was the individual dose of the medication/ therapy? This issue was added	Site unable to complete rSDV