Gan & Lee Pharmaceuticals USA

AN OPEN-LABEL, RANDOMIZED, MULTICENTER, PHASE 3 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

Test Drug: Gan & Lee Insulin Glargine Injection

Protocol Number: GL-GLAT1-3001 **Study Phase:** 3

Protocol Name: Gan & Lee Insulin Glargine Target Type (1) Evaluating Research: GLITTER(1)

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24 March 2017 – Version 1.0

Sponsor:	**Contract Research Organization:**
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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council for Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

SIGNATURES

Representatives of Sponsor and Clinical Research Organization

I have read and agree to the protocol GL-GLAT1-3001 entitled 'An Open-Label, Randomized, Multicenter, Phase 3 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.' I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities.

Protocol Amendment 3 **25 April 2019**

Accepted by the Sponsor – Gan & Lee Pharmaceuticals USA

Lawrence A. Hill, PharmD, MBA, RPh, BCPS	VP, Global Head Clinical Development
Print Name	Title
Lawrence A. Hill	25 Apr 2019
Signature	Date

Jia Lu, MD, PhD	Sr. Director, Clinical Sciences
Print Name	Title
	25 Apr 2019
Signature	Date

Accepted by the Contract Research Organization – PRA Health Sciences:

Kyle Patrick, DO	Medical Director
Print Name	Print Title
Kyle Patrick	30 APR 2019
Signature	Date

Investigator

I have read and agree to the protocol GL-GLAT1-3001 entitled 'An Open-Label, Randomized, Multicenter, Phase 3 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.' I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Protocol Amendment 3 **25 April 2019**

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

Print Name	Title
Signature	Date

1. SYNOPSIS

NAME OF SPONSOR: Gan & Lee Pharmaceuticals USA	**PROTOCOL No.:** GL-GLAT1-3001
NAME OF STUDY TREATMENT: Gan & Lee Insulin Glargine Injection	
TITLE OF STUDY: An Open-label, Randomized, Multicenter, Phase 3 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	
STUDY CENTERS: Approximately 100 sites are planned in the United States and Europe	
STUDY PERIOD: Subjects randomized to the Gan & Lee Insulin Glargine Injection group or the Lantus® group will receive treatment for 26 weeks.	**PHASE OF DEVELOPMENT:** Phase 3
PLANNED STUDY DATES: The study started in 2017 and is expected to end in 2019	

OBJECTIVES:

Primary Objective:

- To evaluate equivalence of Gan & Lee Insulin Glargine Injection and Lantus® in terms of immunogenicity

Secondary Objectives:

- 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®.
- Safety: To evaluate the safety of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus®
- Efficacy: To evaluate the efficacy of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus®

Exploratory Objectives:

- To investigate the retrospective hypoglycemic rate and the 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

STUDY DESIGN AND METHODOLOGY: The purpose of this equivalence study is to compare the immunogenicity, safety, and efficacy of Gan & Lee Insulin Glargine Injection with that of the reference medicinal product, Lantus®, in adult subjects with type 1 diabetes mellitus.

At the screening visit, subjects will sign the informed consent form (ICF), they will be screened for eligibility, and the following information will be collected: adverse events, medical history (including diabetes mellitus and thyroid disease history), prior and concomitant medications, vital signs, height, body weight, and body mass index (BMI). The following procedures will be performed: 12-lead electrocardiogram (ECG), physical examination, and blood collection for fasting blood glucose (FBG) test, glycosylated hemoglobin ($HbA1_c$), AIA, routine hematology and chemistry testing (complete blood count, metabolic chemistry panel with serum lipids, thyroid-stimulating hormone [TSH], and free thyroxine [T4]). A urinalysis, and for women of childbearing potential, a urine pregnancy test will be performed. At this visit, the subject will be issued a glucometer, test strips, and other supplies, and the Investigator or designee will provide instruction and conduct training on how to use the glucometer for prospective capillary blood glucose monitoring to document hypoglycemic episodes in a prospective manner. Subjects will be allowed to keep the glucometer after the study, per local ethical and legal guidelines and regulations. Subjects will also receive a Hypoglycemic Events Record in which they will record information about any hypoglycemic events that occur during their participation in the study. At this visit, the subject will have an Abbott FreeStyle Libre Pro Flash Glucose Monitoring System sensor applied to the back of the upper arm. The

sensor, which calibrates itself during the first 12 to 24 hours after application, will be worn for 8 days and will record the interstitial glucose concentration every 15 minutes. Data from the 2nd through the 8th day of wear will be used for the analysis. The subject will also be issued a Mealtime & Insulin Dose Record for the 8-day period, in which they will record the time of their meals and insulin use. After 8 days, the subject may remove the sensor and bring it to the randomization visit in a provided biohazard bag; if the end of the 8-day CGM period coincides with the date of the randomization visit, the sensor can be removed at the visit by site staff. The information obtained through CGM will have no direct impact on treatment advice and is intended for research purposes only. Subjects will bring both their Hypoglycemic Events Record and their Mealtime & Insulin Dose Record to the randomization visit. Between the screening and randomization visits, subjects will have their basal insulin dose optimized based on their fasting glucose results.

Subjects who meet the study eligibility criteria will be centrally randomized 1:1 in an open-label fashion to receive either Gan & Lee Insulin Glargine Injection or Lantus® for 26 weeks. Randomization will be stratified by country. Subjects will continue using their bolus (short-acting) insulin and will substitute the investigational product (IP) for their long-acting (basal) insulin. In the USA, the Sponsor will ensure that all insulins will be provided to all subjects regardless of medical insurance or reimbursement issues. This applies to the non-study insulins and this should be discussed with the Study Monitor.

At the randomization visit (Visit 2), subjects will receive a supply of insulin pens with IP. The Investigator or designee will train the subject on all study procedures and proper dose administration.

All subjects will attend 9 clinic visits (the screening visit, the randomization visit, and visits at Weeks 2, 4, 8, 12, 16, 20, and 26), 2 brief visits during which a CGM sensor will be applied (8-10 days before the visits at Weeks 12 and 26), 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 visit.

At all visits and phone contacts (except for visits to apply a CGM sensor), the Investigator or designee will review glucose results (especially focusing on hypoglycemia), adverse events, changes in concomitant medications, and changes in IP and bolus insulin use. At all study visits, the following procedures will be performed: vital signs, body weight, urinalysis, urine pregnancy testing for women of childbearing potential, and an FBG test.

Additional procedures at study visits are as follows: at Weeks 8, 16, and 26, blood for $HbA1_c$ will be collected; at Weeks 12 and 26, subjects will wear their CGM sensor to the site for the staff to safely remove it; they will bring their Mealtime & Insulin Dose Record for the site staff to review, and blood will be collected for routine hematology and chemistry, TSH and free T4; at Weeks 12 and 26, blood will be collected for AIA; and at Week 26, a 12-lead ECG and physical examination will be performed. A subset of additionally consented subjects will have blood drawn at Day 1 and Weeks 2, 4, 8, 12, 16, 20, and 26 for optional pharmacokinetics (PK) (insulin glargine, M1, and M2 concentrations).

If a subject discontinues the study prematurely (early termination – ET), site personnel will make a reasonable effort to perform all study activities scheduled for Visit 9 (end of treatment – EOT visit). Additionally, it is also very important for site personnel to encourage subjects to visit the site at Week 26 $\pm$ 4 weeks (and Week 12 $\pm$ 1 week, if applicable) for a blood sample to be obtained for AIA and $HbA1_c$ measurements.

Site personnel will contact the subjects by telephone approximately 30 days after study completion to query for serious adverse event information only.

Subjects will only be included in the optional PK portion of the study if they are able to provide a baseline PK sample.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:
Subjects cannot be enrolled or randomized until all inclusion criteria (including test results) are confirmed.

Inclusion Criteria:

1. Male or nonpregnant, nonlactating female subjects between the ages of 18 and 75 years, inclusive
2. Ability to provide written, personally signed, and dated informed consent to participate in the study, in accordance with the ICH GCP Guideline E6 and all applicable regulations, before initiating any

study-related procedures

3. Ability to understand and fully comply with all study procedures and restrictions
4. Subjects with a confirmed diagnosis of type 1 diabetes mellitus who have been on an approved basal and bolus insulin regimen for at least 6 months (the type or brand of insulin should not have changed in the 6 months before screening)
5. $HbA1_c \leq 11.0\%$
6. BMI ≥ 19 kg/m^2 and ≤ 35 kg/m^2
7. Adherence to a prudent diet and exercise regimen recommended by the medical provider, and willingness to maintain these consistently for the duration of the study
8. Concomitant medications are allowed, provided that no significant dosing changes are anticipated during the study (see the exclusion criteria below for specific prohibited concomitant medications); for concomitant thyroid medications, subjects must have been on a stable dosage for 90 days before screening

Exclusion Criteria:

1. Participation in another clinical study or use of any study drug within 30 days before screening
2. Previous use of a biosimilar insulin, either basal or bolus
3. Diabetic ketoacidosis within a year before screening
4. 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)
5. 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
6. Anticipated change in insulin used during the study (change in dosage is allowed, but change in type or brand of insulin will result in the subject being withdrawn from the study)
7. Inadequately controlled thyroid disease, defined as a TSH or free T4 value > the upper limit of normal
8. BMI < 19 kg/m^2 or > 35 kg/m^2
9. Any clinically significant (in the opinion of the Investigator) hematology or chemistry test results at screening, including any liver function test > 3x the upper limit of normal (subjects with elevated bilirubin due to Gilbert syndrome are eligible to participate)
10. Documented history of anti-insulin antibodies
11. Treatment with glucocorticosteroids, immunosuppressants, or cytostatic agents within 60 days before screening (newly-prescribed or high-dose corticosteroids are prohibited; chronically administered oral, inhaled, topical, or intra-articular corticosteroids at a stable dosage are allowed if no increase in dose is anticipated during the study; See Appendix 3 [Section 17.3] for a list of allowed and prohibited medications)
12. Current use of medication intended to cause weight loss or weight gain
13. Alcohol or substance use disorder within the 2 years before screening
14. Any previous or anticipated treatment with interferons
15. Any history of malignant disease within 5 years before screening, except for adequately treated basal cell carcinoma
16. Severe concomitant physical or psychiatric diseases or conditions
17. A history of a positive test result for HIV, hepatitis B, or hepatitis C; any subject who has a positive test result during the study may continue at the discretion of the Investigator
18. Any history of pancreatitis or pancreatectomy
19. 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

20. Any condition e.g., splenectomy, autoimmune disease, or rheumatologic disease, that could affect immunologic responses, could indicate an altered immune system, or could require treatment with a prohibited medication
21. 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)
22. Any other 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
23. Intolerance or history of hypersensitivity to insulin glargine or any excipient of IP
24. Inability or unwillingness 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

NUMBER OF SUBJECTS: Enrollment is planned for 550 subjects overall (275 subjects per treatment group). The primary analysis for immunogenicity will be an equivalence test using the 2 one-sided tests (TOST) approach with α=0.05. This sample size was chosen to achieve over 80% power on the equivalence test under margins dependent on the observed treatment-induced AIA rate. Sample size calculations were performed using EAST Version 6.4.

STUDY TREATMENT(S):
Test Product, Dose and Mode of Administration: Gan & Lee Insulin Glargine Injection for subcutaneous injection, 100 U/mL, in the integrated, disposable 3.0-mL pre-filled Gan & Lee injector pen

Reference Therapy, Dose and Mode of Administration: Lantus® (insulin glargine injection) solution for subcutaneous injection, 100 U/mL, in the SoloStar® 3-mL pre-filled insulin pen

Lantus® contains insulin glargine, an insulin analog, and has a prolonged duration of action. Lantus® and Gan & Lee Insulin Glargine should be administered once daily at any time but at the same time each day. To be consistent with current Lantus® labeling, twice-daily dosing of IP is strictly prohibited. The dose regimen (dose and timing) should be individually adjusted.

DURATION OF TREATMENT: Subjects in both groups will receive study treatment for 26 weeks

STUDY EVALUATIONS:
Primary Endpoint:

- **Immunogenicity:** The percentage of subjects in each treatment group who develop treatment-induced AIA, defined as treatment-emergent AIA development or important (at least 4-fold) increase in titers and up to visit Week 26

Key Secondary Endpoint:

- **Efficacy:** The change in $HbA1_c$ from baseline at visit Week 26

Other Secondary Endpoints:

- **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
  - 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

- **Safety:**
  - The incidence and severity of all treatment-emergent adverse events and the following subgroups:
    - Hypoglycemia, which will be fully documented prospectively in the Hypoglycemic Events Record
    - Serious adverse events, including fatal events
    - Adverse events leading to termination of the study treatment and/or early withdrawal from the study
    - IP-related adverse events
    - Injection site reactions
  - The incidence of clinically significant laboratory abnormalities
  - The incidence of clinically significant abnormalities in ECG and vital signs
- **Efficacy:**
  - 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 $HbA1_c$ of < 7.0% at visit Week 26

Exploratory Endpoints:

- Retrospective CGM hypoglycemic rate
- Time in hypoglycemia and hyperglycemia
- Relationship between plasma concentrations of insulin glargine, M1, and M2, and AIA titers

STATISTICAL METHODS:

The primary analysis for immunogenicity will be an equivalence test using the TOST approach with α=0.05 via a normal test of difference in proportions to (-margin, +margin) where the margin is dependent on the observed treatment-induced AIA rate in Lantus®. The number and percentage of subjects in each treatment group who develop treatment-induced AIA after baseline and up to visit Week 26 will be evaluated using a test for difference in proportions based on the normal approximation. The difference in proportions will be estimated along with the corresponding 90% CI in the Safety Analysis Set using Wald method for risk difference without continuity correction. The estimand of interest for the primary immunogenicity analysis is the difference in treatment-induced immunogenicity 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).

The key secondary analysis will be to evaluate equivalence (FDA)/noninferiority (EMA) of Gan & Lee Insulin Glargine Injection relative to Lantus® for $HbA1_c$ by comparing the 90% confidence interval with (-0.4%, 0.4%) for equivalence using the TOST approach and by comparing the upper limit of the 95% CI with 0.4% for noninferiority from a pattern mixture model that uses multiple imputation analyzed using Analysis of Covariance (ANCOVA) with treatment and stratification factor of country included as fixed effects and baseline $HbA1_c$ included as a covariate. Separately in each treatment group, the imputation will use the outcomes of patients who completed the study (including subjects who discontinued treatment but provided a visit Week 26 HbA1c sample) to impute outcomes in patients without actual visit Week 26 recorded results under the missing at random assumption. Full details of the multiple imputation procedure will be specified in the SAP. Analysis of $HbA1_c$ will follow a hierarchical testing strategy: first, equivalence/noninferiority will be tested with a margin of 0.4%; secondly, if and only if the test using a margin of 0.4% is significant, then equivalence/noninferiority will be tested using a margin of 0.3%. Analyses of $HbA1_c$ in the testing hierarchy will be conducted on the Full Analysis Set consisting of all randomized subjects according to randomized treatment with supportive analyses on the Per Protocol Analysis Set. A tipping point analysis with varying assumptions about the differences on each treatment arm between outcomes in patients who withdrew from the study early and outcomes in patients who completed the study will be performed.

Categorical variables will be summarized using counts and percentages. Continuous variables will be

summarized using the number of observations, mean, standard deviation, median, minimum and maximum.

The secondary immunogenicity variables of the percentage of subjects with negative AIA at baseline who develop confirmed positive AIA up to visit Week 26 and the percentage of subjects with confirmed positive AIA after baseline and up to Week 26 will be compared between treatment groups using a normal test of difference in proportions. The difference in proportions will be estimated along with the corresponding 90% CI using Wald method for risk difference without continuity correction. The secondary immunogenicity variables of 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 and the percentage of subjects 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, will be compared between treatment groups using an exact test of difference in proportions. The difference in proportions will be estimated along with the corresponding 90% CI in the Safety Analysis Set. The exact confidence limits are computed by inverting 2 separate one-sided exact tests that are based on the score statistic. The mean change from baseline in each treatment group in AIA titers after baseline and up to visit Week 26 will be tabulated descriptively.

Safety variables will be summarized descriptively in the Safety Analysis Set consisting of all randomized subjects according to actual treatment received. All reported adverse events will be assigned a system organ class and preferred term according to the Medical Dictionary for Regulatory Activities and graded according to Common Toxicity Criteria for Adverse Events version 4.03. The number and percentage of subjects with adverse events (all adverse events, hypoglycemia, serious adverse events [including fatal], adverse events leading to termination of study treatment and/or early withdrawal from the study, IP-related adverse events, and injection site reactions) will be presented. Vital signs, body weight and BMI, ECG, and laboratory results will be summarized by treatment and visit.

The secondary efficacy variables of number and percentage of subjects achieving a $HbA1_c$ value < 7.0% at visit Week 26 and the number and percentage of subjects achieving a FBG test result of ≤ 6.0 mmol/L (≤ 108.0 mg/dL) in each treatment group will be compared using a test of difference of proportions based on the normal approximation and confidence intervals. The retrospective CGM hypoglycemic rate and time in hypoglycemia and hyperglycemia will be summarized for subjects in the Safety Analysis Set. The plasma concentrations of insulin glargine, M1, and M2 will be plotted against AIA titers.

DATE AND VERSION: 25 April 2019; Amendment 3

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AIA	Anti-Insulin Antibody
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCCT	Diabetes Control and Complications Trial
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of treatment
FAS	Full Analysis Set
FBG	Fasting Blood Glucose
FDA	Food and Drug Administration
GCP	Good Clinical Practice
$HbA1_c$	Glycosylated Hemoglobin (Glycated Hemoglobin)
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IXRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NPH	Neutral Protamine Hagedorn
PK	Pharmacokinetic
PP	Per Protocol
PRA	Pharmaceutical Research Associates (PRA Health Sciences)
QTL	Quality tolerance limit
SAP	Statistical Analysis Plan
TOST	2 One-sided Tests
TSH	Thyroid-Stimulating Hormone

Term	Definition
US/USA	United States/United Sates of America
WHO	World Health Organization
WMA	World Medical Association

4. ETHICS

4.1 Ethics Committee

4.1.1 Europe

This study will be conducted in compliance with Independent Ethics Committee (IEC) and International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IEC for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects and a statement from the IEC that these materials comply with GCP requirements. The IEC approval must identify the protocol version as well as the documents reviewed.

4.1.2 United States

This study will be conducted in compliance with institutional review board (IRB) and ICH GCP Guidelines - including Title 21 Part 56 of the United States of America (USA) Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the United States Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B(R3)), and with ICH regulations regarding scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB for the study protocol/amendment(s), written ICF, any consent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects and a statement from the IRB that these materials comply with GCP requirements. The IRB approval must identify the protocol version as well as the documents reviewed.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); FDA CFR (21 CFR § 50, 56, 312)), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC, the general guidelines indicated in the Declaration of Helsinki (Seoul 2008) (Appendix 1, Section 17.1) and all applicable regulatory requirements.

4.3 Subject Information and Consent

The Investigator will explain the benefits and risks of participation in the study to each subject, the subject's legally acceptable representative, or impartial witness, and obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of investigational product [IP]).

The Sponsor will provide a sample ICF, based on the elements of informed consent in Appendix 2 (Section 17.2). The final, version-dated form must be agreed to by the Sponsor and the IRB/IEC and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the consent of the subject. In this instance, approval should always be given by the IRB/IEC and existing subjects informed of the changes and reconsented. This is documented in the same way as previously described.

5. STUDY ADMINISTRATIVE STRUCTURE

Sponsor:

Gan & Lee Pharmaceuticals USA
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Specialty Laboratory (PK): Arcinova
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Interactive Web Response System (IXRS):

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Doylestown, PA 18901, USA

Clinical Study Medication Management:

Almac Group Global & EU Headquarters
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Craigavon BT63 5QD, UK
Almac Group US Headquarters
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Souderton, PA 18964, USA

Clinical Study Equipment Management:

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1360 South Loop Road,
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Continuous Glucose Monitoring Data Capture:

Precision Digital Health, Inc.
15615 Alton Pkwy
Irvine, CA 92618, USA

6. INTRODUCTION

6.1 Disease Review

Type 1 diabetes usually results from cellular autoimmune destruction of the beta cells in the pancreas, severely reducing or eliminating production of endogenous insulin. Without insulin, glucose cannot enter cells and blood glucose concentration increases. Hepatic gluconeogenesis may ensue, further elevating the blood glucose concentration. Without treatment, potentially life-threatening ketoacidosis may develop [1].

Diabetes is a chronic, progressive disease that, if inadequately treated, can lead to significant morbidity, including macrovascular and microvascular complications, and significantly increased mortality. In conjunction with ongoing patient lifestyle education regarding self-management of the disease, subcutaneous insulin is the mainstay of treatment for patients with type 1 diabetes [1].

The Diabetes Control and Complications Trial (DCCT) [2] demonstrated that intensive therapy with subcutaneous insulin leads to improved glycemic control and better outcomes. Since the publication of the DCCT, several insulin analogs have been developed that are associated with a lower risk of hypoglycemia in patients with type 1 diabetes and lowering of glycosylated hemoglobin ($HbA1_c$) equivalent to human insulin [2]. Ratner et al [3] showed that compared with human insulin, treatment with insulin glargine was associated with lower fasting glucose concentrations and a lower incidence of hypoglycemia. Hasslacher et al [4] showed that subjects with type 1 diabetes and early stage chronic kidney disease who were treated with insulin analogs such as insulin glargine had better kidney function and higher hemoglobin concentrations, compared with those who received human insulin.

6.2 Compound Review – Insulin Glargine

Insulin glargine is a biosynthetic insulin analog with a longer duration of action than human insulin. The substitution of glycine for asparagine at A21 and the addition of 2 arginines at the C-terminus of the B chain result in stabilization of the molecule, leading to delayed and prolonged absorption after subcutaneous injection [3, 5].

6.2.1 Nonclinical Studies

An extensive characterization and comparison of structural and biofunctional properties of Gan & Lee Insulin Glargine Injection and Lantus® has been conducted [6]. The structural characterization (including primary, secondary, tertiary and quaternary structures; size, hydrophobicity, charge heterogeneities, and cell-based biofunctionality including the binding to the receptors of insulin and insulin-like growth factor-1), and the activation of the insulin-signaling cascade and the stimulation of glucose uptake were demonstrated to be similar between Gan & Lee Insulin Glargine Injection and Lantus®. For in vitro and in vivo pharmacologic and toxicologic studies and clinical studies, reference is made to NDA 021081 [5].

6.2.2 Clinical Studies

In 2016, Study GL-GLA-001, a phase I, exploratory, randomized, double-blind, 2-way crossover pilot study, demonstrated bioequivalence of Gan & Lee Insulin Glargine Injection and United States (US)-sourced Lantus®. Although this exploratory study suggested biosimilarity, it was not powered to provide robust statistical conclusions. Gan & Lee Insulin Glargine Injection was well tolerated, and treatment-emergent adverse events were comparable to those with Lantus®. There were no significant signals that would indicate a difference in the safety profile between the treatments. A pivotal phase I study will be performed concurrently to assess the pharmacokinetic (PK) and pharmacodynamic effects of Gan & Lee Insulin Glargine Injection compared with US- and European-sourced Lantus®.

6.3 Clinical Study Rationale

The purpose of this study is to compare Gan & Lee Insulin Glargine Injection 100 U/mL with that of the reference medicinal product, Lantus®, Sanofi-Aventis' brand of insulin glargine injection 100 U/mL, and evaluate equivalence in terms of immunogenicity, safety, and efficacy, in subjects with type 1 diabetes mellitus.

Insulin analogs are more costly than conventional insulins, and limited access to affordable insulin may keep some patients from accessing important treatment options, leading to unnecessary complications [1, 7].

Biosimilar products may result in significant price reductions compared to the cost of the reference products, even if the reductions are not of the magnitude seen with many generics [8].

Biosimilar drugs are not identical to the reference product. Because even small differences in the primary structure can result in clinically significant functional differences, there are concerns about potential risks to patients [8]. Insulin glargine has been shown to exhibit proliferative and anti-apoptotic effects in vitro in colorectal cancer cells; however, clinical studies have produced conflicting results regarding an association between insulin glargine and cancer risk [9]. And although a number of observational studies in 2009 found an association between insulin glargine and an increased risk for breast cancer in patients with type 2 diabetes, a recent study of more than 12,000 subjects with type 2 diabetes who were newly started on insulin glargine showed no increase in the risk of breast cancer after a median 5-year follow-up period among those who were insulin-naïve. A nonsignificant increase in risk was found among subjects who had switched to insulin glargine from other insulins [10].

Because biosimilar insulins have immunogenic potential, the European Medicines Agency (EMA) and the FDA require an evaluation of safety and immunogenicity between biosimilars and their reference products, and the EMA has indicated these studies should be of sufficient duration (at least 6 to 12 months) to detect these differences. This study is designed in accordance with the guidance documents provided by the EMA [11] and the FDA [12].

The immunogenicity assessment will use the one-assay [13] and tiered approach [14]. Samples collected at all time points (including pre-dose) from both treatment groups will first be tested using the validated electrochemiluminescence method [15]. The rate and degree of immunogenicity, and data interpretation will also include consideration of other clinical attributes such as (but not limited to) symptoms of hypersensitivity or injection site reactions and the PK profile.

7. STUDY OBJECTIVES

7.1 Primary Study Objective:

- To evaluate equivalence of Gan & Lee Insulin Glargine Injection and Lantus® in terms of immunogenicity

7.2 Secondary Study Objectives:

7.2.1 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 the percentage of subjects in each treatment group with confirmed positive AIA up to visit Week 26 of Gan & Lee Insulin Glargine Injection in comparison with that of Lantus®

7.2.2 Safety

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

7.2.3 Efficacy

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

7.3 Exploratory Study Objectives:

- To investigate the retrospective hypoglycemic rate and the 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

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

The purpose of this equivalence study is to compare the immunogenicity, safety, and efficacy of Gan & Lee Insulin Glargine Injection with that of the reference medicinal product, Lantus®, in adults with type 1 diabetes mellitus.

At the screening visit, subjects will sign the informed consent form (ICF), they will be screened for eligibility, and the following information will be collected: adverse events, medical history (including diabetes mellitus and thyroid disease history), prior and concomitant medications, vital signs, height, body weight, and body mass index (BMI). The following procedures will be performed: 12-lead electrocardiogram (ECG), physical examination, and blood collection for fasting blood glucose (FBG) test, $HbA1_c$, AIA, and routine hematology and chemistry testing (complete blood count, metabolic chemistry panel with serum lipids, thyroid-stimulating hormone [TSH], and free thyroxine [T4]). A urinalysis, and for women of childbearing potential, a urine pregnancy test will be performed. At this visit, the subject will be issued a glucometer, test strips, and other supplies, and the Investigator or designee will provide instruction and conduct training on how to use the glucometer for prospective glucose monitoring to document hypoglycemic episodes in a prospective manner. Subjects will be allowed to keep the glucometer after the study, per local ethical and legal guidelines and regulations. Subjects will also receive a Hypoglycemic Events Record in which they will record information about any hypoglycemic events that occur during their participation in the study.

During the 2 weeks between screening and randomization, subjects will have their insulin dosing optimized according to Table 3 in Section 8.5.8.

Also, at the screening visit, the subject will have a FreeStyle Libre Pro Flash Glucose Monitoring sensor applied to the back of the upper arm according to the manufacturer's instructions.

The FreeStyle Libre Pro Flash Monitoring System is approved by the EMA for people 18 years of age or older with diabetes. The FreeStyle Libre Pro Flash Glucose Monitoring System sensor, which requires 12 to 24 hours to calibrate itself after application, will be worn for 8 days and will record the interstitial fluid glucose every 15 minutes. Data from the 2nd through the 8th days of wear will be used for each analysis. The sensor will be blinded to the subject and no subject action will be needed. The subject will also be issued a Mealtime & Insulin Dose Record in which they will record the time of their meals, and insulin use. After 8 days, the subject may remove the sensor, place in the biohazard bag provided and bring it with them to the randomization visit. If the end of the 8-day continuous glucose monitoring (CGM) period coincides with the date of the randomization visit, the sensor can be removed at the visit. Subjects will bring both their Hypoglycemic Events Record and their Mealtime & Insulin Dose Record to the randomization visit.

Subjects who meet the study eligibility criteria will be centrally randomized 1:1 in an open-label fashion to receive either Gan & Lee Insulin Glargine or Lantus® for 26 weeks. Randomization will be stratified by country. Subjects will continue using their bolus insulin

but will substitute IP for their basal insulin. The Sponsor will ensure that all insulins will be provided to all subjects regardless of medical insurance or reimbursement issues.

At the randomization visit (Visit 2), subjects will receive supply of insulin kits with 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 (telephone call); and then at Week 26; they will attend a total of 9 clinic visits (the screening visit, the randomization visit, and at Weeks 2, 4, 8, 12, 16, 20, and 26), 2 brief visits during which a CGM sensor will be applied (8-10 days before the visits at Weeks 12 and 26), 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 visit.

At all planned visits and phone contacts (except for visits to apply a CGM sensor) the Investigator or designee will review glucose results (especially looking for hypoglycemia), adverse events, changes in concomitant medications, and changes in IP or bolus insulin use, and the following procedures will be performed: vital signs, body weight, urinalysis, urine pregnancy testing for women of childbearing potential, and an FBG test.

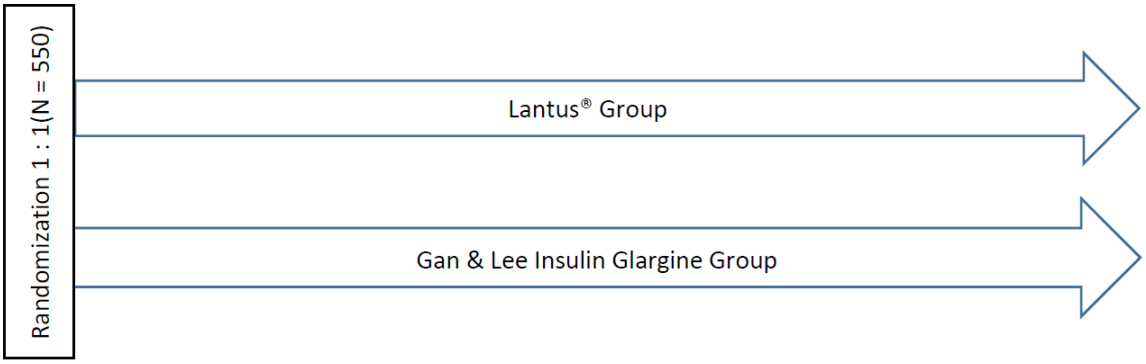
Additional procedures at study visits are as follows: at Weeks 8, 16 and 26, blood for $HbA1_c$ will be collected; during the visits at Weeks 12 and 26, subjects will wear their CGM sensors to the site for the site staff to safely remove it, and they will bring their Mealtime & Insulin Dose Record for the site staff to review, and blood will be collected for routine hematology and chemistry testing, TSH and free T4 and TSH; at Weeks 12 and 26, blood will be collected for AIA; and at Week 26, a 12-lead ECG and physical examination will be performed.

A subset of additionally consented subjects will have blood drawn at Day 1 and Weeks 2, 4, 8, 12, 16, 20, and 26 for optional PK (insulin glargine, M1, and M2 concentrations).

If a subject discontinues the study prematurely, site personnel will make a reasonable effort to perform all study activities scheduled for Visit 9 (end of treatment [EOT] visit). Additionally, it is very important for site personnel to encourage subjects to visit the site at Week 26 (± 4 weeks) (and Week 12 ± 1 week if applicable) for a blood sample to be obtained for AIA and $HbA1_c$ measurements.

Figure 1 and Table 1 show the study design and study-related procedures, respectively.

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.

Table 1: 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 days ±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	
HbA1$_c$	X					X					X					X	
Pre-dose Blood Sample for AIA	X								X							X	
Optional Pre-dose PK Blood Sample for Insulin Glargine, M1, M2		X	X	X		X			X		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 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; HbA1$_c$ = glycosylated hemoglobin; IP = investigational product; PK = pharmacokinetic; TC = telephone call; UA - urinalysis

[a] Any subject who withdraws from the study before Week 26 will perform all study activities scheduled for Visit 9 (EOT visit). Additionally, it is very important for site personnel to encourage subjects to visit the site at Week 26 (± 4 weeks) (and Week 12 ± 1 week if applicable) for a blood sample to be obtained for AIA and HbA1c measurements

[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, and 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: Following the screening visit, subjects will have their insulin dosing optimized as described in Section 8.5.8.

8.2 Discussion of Study Design

This open-label study is designed to evaluate Gan & Lee Insulin Glargine Injection compared with that of Lantus® in subjects with type 1 diabetes to determine equivalence. Randomization will be stratified by country. Subjects will continue using their bolus insulin (which should not be changed for the duration of the study, with the exception of a dose change) and will substitute IP for their basal insulin.

8.3 Study Duration

Subjects will participate for 26 weeks. Recruitment will stop when approximately 275 subjects have been randomized to each treatment group. The study will end when the last subject completes the end-of-treatment visit, or discontinues the study treatment, whichever occurs first.

This study duration has been used in comparisons between other biosimilar long-acting insulin analogs and their reference products.

8.4 Study Population

The study population will be selected from subjects with type 1 diabetes who meet all the inclusion criteria and none of the exclusion criteria. Subject race and ethnicity will be collected according to FDA guidance [16].

8.4.1 Inclusion Criteria

Subjects must satisfy all of the following entry criteria before they will be allowed to participate in the study:

1. Male or nonpregnant, nonlactating female subjects between the ages of 18 and 75 years, inclusive
2. Ability to provide written, personally signed, and dated informed consent to participate in the study, in accordance with the ICH GCP Guideline E6 and all applicable regulations, before initiating any study-related procedures
3. Ability to understand and fully comply with all study procedures and restrictions.
4. Subjects with a confirmed diagnosis of type 1 diabetes mellitus who have been on an approved basal and bolus insulin regimen for at least 6 months (the type or brand of insulin should not have changed in the 6 months before screening)
5. $HbA1_c \leq 11.0\%$
6. Body mass index (BMI) ≥ 19 kg/m^2 and ≤ 35 kg/m^2
7. Adherence to a prudent diet and exercise regimen recommended by the medical provider, and willingness to maintain these consistently for the duration of the study
8. Concomitant medications are allowed, provided that no significant dosing changes are anticipated during the study (see the exclusion criteria below and Appendix 3 (Section 17.3) for specific allowed and prohibited concomitant medications); for

concomitant thyroid medications, subjects must have been on a stable dosage for 90 days before screening

8.4.2 Exclusion Criteria

1. Participation in another clinical study or use of any study drug within 30 days before screening
2. Previous use of a biosimilar insulin, either basal or bolus
3. Diabetic ketoacidosis within a year before screening
4. 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)
5. 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
6. Anticipated change in insulin used during the study (change in dosage is allowed, but change in type or brand of insulin will result in the subject being withdrawn from the study)
7. Inadequately controlled thyroid disease, as reflected by a TSH value or free T4 > the upper limit of normal
8. BMI < 19 kg/m^2 or > 35 kg/m^2
9. 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 (subjects with elevated bilirubin due to Gilbert syndrome are eligible to participate)
10. Documented anti-insulin antibodies in the past
11. Treatment with glucocorticosteroids, immunosuppressants, or cytostatic agents within 60 days before screening (newly-prescribed or high-dose corticosteroids are prohibited; chronically administered oral, inhaled, topical, or intra-articular corticosteroids at a stable dosage are allowed if no increase in dose is anticipated during the study; see Appendix 3 [Section 17.3] for a list of allowed and prohibited medications)
12. Current use of medication intended to cause weight loss or weight gain
13. Alcohol or substance use disorder within the 2 years before screening
14. Any previous or anticipated treatment with interferons
15. Any history of malignant disease within 5 years before screening, except for adequately treated basal cell carcinoma
16. Severe concomitant physical or psychiatric diseases or conditions
17. A history of a positive test result for HIV, hepatitis B, or hepatitis C; any subject who has a positive result during the study may continue at the discretion of the Investigator
18. Any history of pancreatitis or pancreatectomy

19. 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
20. Any condition e.g., splenectomy, autoimmune disease, or rheumatologic disease, that could affect immunologic responses, could indicate an altered immune system, or could require treatment with a prohibited concomitant medication
21. 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)
22. Any other 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
23. Intolerance or history of hypersensitivity to insulin glargine or any excipient of IP
24. Inability or unwillingness 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

8.4.3 Withdrawal and Replacement of Subjects

8.4.3.1 Criteria for Subject Withdrawal

In accordance with the Declaration of Helsinki (Appendix 1, Section 17.1) and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Subjects may also be withdrawn from the study for any of the following reasons:

- The Investigator decides that the subject should be withdrawn. If this decision is made because of an intolerable adverse event or a clinically significant laboratory abnormality, the study medication is to be discontinued and appropriate treatment is to be provided. The Sponsor or designee is to be notified immediately.
- The subject requires a change in the type or brand of insulin (other than a change in dosage)
- The subject is unwilling to continue in the study
- Lack of compliance with protocol
- The Investigator or the Sponsor stops the study per Section 15.8
- The subject fails to respond to the study medication at an acceptable level, and the subject or Investigator determine another treatment is preferable.
- The subject fails to return to the clinic for scheduled visits and does not respond to telephone calls or written attempts at communication.

- If a subject becomes pregnant during the study, she will discontinue IP immediately, report the pregnancy to the Investigator, and attend an end-of-treatment visit. If the female partner of a male subject becomes pregnant, the subject may continue in the study, but the pregnancy should be reported. See Section 11.7 of this document for more details about pregnancy reporting procedures.

The reason for withdrawal will be recorded in the clinical records and the electronic Case Report Form (eCRF). All subjects who are withdrawn from the study will attend an end-of-treatment clinic visit (see Section 9.10). All subjects who are withdrawn from the study should be offered appropriate follow-up medical care.

8.4.3.2 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

8.5 Treatment

8.5.1 Treatments Administered

Subjects will be randomized to receive either Lantus® or Gan & Lee Insulin Glargine Injection for subcutaneous injection. Details of each product are shown in Table 2.

Table 2: Identity of the Investigational Medicinal Products

Drug name	Gan & Lee Insulin Glargine Injection	Lantus®
Manufacturer	Gan & Lee Pharmaceuticals, China	Sanofi-Aventis Deutschland GmbH, Germany
Formulation	Solution	Solution
Strength	100 U/mL	100 U/mL
Route of administration	Subcutaneous	Subcutaneous

Lantus® contains insulin glargine, an insulin analog, and has a prolonged duration of action. Lantus® and Gan & Lee Insulin Glargine should be administered once daily at any time but at the same time each day. To be consistent with current Lantus® labeling, twice-daily dosing of IP is strictly prohibited. The dose regimen (dose and timing) should be individually adjusted.

Gan & Lee Insulin Glargine Injection will be contained in Gan & Lee injector pens (3.0-mL pre-filled glass cartridge) for multiple dose administration.

Lantus® will be provided in 3.0-mL SoloStar® pre-filled pens.

Subjects will follow instructions provided by the Investigator and/or designee regarding proper dose administration of IP and use of the insulin pens, glucometer and related supplies, and the frequency of glucose testing.

8.5.2 Study Treatment Formulation

8.5.2.1 Gan & Lee Insulin Glargine Injection

The experimental drug is Gan & Lee Insulin Glargine Injection manufactured by Gan & Lee Pharmaceuticals (Beijing, China). This formulation is a clear, colorless, sterile solution for subcutaneous injection, and the concentration is 100 U/mL.

8.5.2.2 Lantus®

The active comparator, Lantus® (insulin glargine injection) solution for subcutaneous injection, is a long-acting insulin analog manufactured by Sanofi-Aventis. This formulation is a clear, colorless, sterile solution, and the concentration is 100 U/mL.

8.5.3 Dose and Administration of the Investigational Product

The dosage of IP should be determined by the physician, according to the requirement of the subject. Insulin glargine preparations should be given by subcutaneous injection only.

Subcutaneous administration should be in the upper arms, thighs, buttocks, or abdomen. Injection sites should be rotated according to clinical practice.

When administered subcutaneously, care should be taken when injecting insulin glargine to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged.

8.5.4 Study Treatment Labeling and Packaging

Both Gan & Lee Insulin Glargine Injection and Lantus® will be supplied and appropriately labeled in accordance with all national and local regulatory requirements.

8.5.5 Blinding of Study Medication

Not applicable to this open-label study

8.5.6 Study Treatment Storage and Accountability

8.5.6.1 Study Treatment Storage

Investigative product must be kept in an appropriate, limited-access, secure location. The storage area should be labeled "For Investigational Use." The Investigator or designee must maintain a log of temperature for the refrigerator in which IP is stored and must record and evaluate the temperature of the storage site in accordance with all applicable standards.

Gan & Lee Insulin Glargine Injection

Before opening, store Gan & Lee Insulin Glargine Injection in a refrigerator at 36 to 46º F (2 to 8°C). Do not freeze or place next to the freezer or a freezer pack. Keep the unopened Gan & Lee Insulin Glargine Injection pens in the outer carton to protect from light. After its first use, the pen must be stored not above 30°C (86ºF), for a maximum of 4 weeks. Do not refrigerate. Keep the pen protected from light.

Lantus®

Lantus® should not be stored in the freezer and should not be allowed to freeze. Discard Lantus® if it has been frozen. Protect Lantus® from direct heat and light. Unopened Lantus® that is not in use should be stored refrigerated at 36° to 46°F (2° to 8°C). After a Lantus® SoloStar® insulin pen is opened and in use, it should be stored at room temperature below 86°F (30°C) for a maximum of 28 days. Once opened, the Lantus® SoloStar® pen should not be refrigerated.

8.5.6.2 Study Treatment Accountability

The Investigator is required to document the receipt, issue, and return or destruction of IP provided by the Sponsor, in accordance with GCP.

No IP may be dispensed to any person not enrolled in the study. The Investigator or designee will count and reconcile drug supplies at the site before either returning them to Gan & Lee Pharmaceuticals or designee at the end of the study.

8.5.7 Gan & Lee Insulin Glargine Injection Pen and the Lantus® SoloStar®

The Gan & Lee Insulin Glargine Injection pen and the Lantus® SoloStar® are disposable, multiple-dose, "dial and push"-type variable dose pens intended for the subcutaneous administration of insulin. The injector pen and the drug product (in a 3.0-mL pre-filled glass cartridge) form a single integral product and will be used in conjunction with needles in a suitable range of sizes to be determined by the Investigator's team. The 3-mL pre-filled glass cartridge contains 300 units of insulin and a maximum deliverable dose of 1 to 80 units with a dose increment of 1 unit. The Investigator or designee will train subjects regarding proper use and handling of the insulin pen injectors for the study and instruct subjects to bring used insulin kits to clinic visits when all the pens in a kit have been used. At the end-of-treatment visit, subjects will bring all used and unused kits to the clinic.

8.5.8 Dose Adjustments and Dose Escalation

The Investigator will develop each subject's treatment plan and instruct the subject regarding dosing of all their medications, including IP. During the 2-week period between the screening and randomization visits, subjects will have their current basal insulin dose optimized based on fasting glucose results according to Table 3. Optimizing the dose before the randomization visit will reduce the need for dose adjustments during the study. Subjects will follow the instructions provided by the Investigator regarding any dose adjustments and other details regarding the clinical management of glucose and insulin.

Table 3: Basal Insulin Dose Adjustment Based on Fasting Glucose Result

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

8.5.9 Initiating Therapy

8.5.9.1 Switching from Other Insulins to Insulin Glargine

When switching from a treatment regimen with an intermediate- or long-acting insulin to a regimen with insulin glargine, a change of the dose of the basal insulin may be required and the concomitant treatment for diabetes may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogs).

8.5.9.2 Switching from Twice-Daily Isophane (Neutral Protamine Hagedorn [NPH]) Insulin to Insulin Glargine

To reduce the risk of nocturnal and early morning hypoglycemia, subjects who are changing their basal insulin regimen from a twice-daily NPH insulin to a once-daily regimen with insulin glargine should reduce their daily dose of basal insulin by 20% to 30% during the first weeks of treatment.

8.5.9.3 Hypoglycemia

The time of occurrence of hypoglycemia may change with a change of insulin regimen, depending on the action profile of the insulins used. Because Lantus® has a more sustained basal insulin supply, fewer nocturnal but more frequent early morning episodes of hypoglycemia can be expected. Particular caution should be exercised, and intensified blood glucose monitoring is advisable for subjects in whom hypoglycemic episodes might be of particular clinical relevance, such as subjects with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycemia), and for subjects with proliferative retinopathy, particularly if they have not been treated with photocoagulation (risk of transient amaurosis following hypoglycemia).

Subject adherence to the prescribed medication, diet, and exercise regimens; correct insulin administration; and awareness of symptoms are essential to reduce the risk of hypoglycemia. The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycemia. If normal or decreased $HbA1_c$ values are noted, the Investigator should consider the possibility of recurrent, unrecognized (especially nocturnal) episodes of hypoglycemia.

Investigators will advise each subject about circumstances in which warning symptoms of hypoglycemia may be different, diminished, or absent, and that hypoglycemia (and possible loss of consciousness) may occur before the subject is aware of any symptoms.

Some factors that may increase the susceptibility to hypoglycemia and require particularly close monitoring and possible dose adjustment include:

- Markedly improved glycemic control after starting the study treatment
- A known tendency to gradually develop hypoglycemia
- Older subject age
- Switching from animal insulin to human insulin
- Autonomic neuropathy

- A long history of diabetes
- Psychiatric illness
- A change in the site of injection from one body area to another
- Conditions that may improve insulin sensitivity such as decreased stress
- Unusual, increased, or prolonged physical activity
- Intercurrent illness such as vomiting or diarrhea
- Inadequate intake of food and/or liquids
- Missed meals
- Alcohol consumption
- Uncompensated endocrine disorders such as hypothyroidism, anterior pituitary or adrenocortical insufficiency
- Concomitant medications that may enhance the blood glucose-lowering effect and increase susceptibility to hypoglycemia, such as angiotensin converting-enzyme inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, propoxyphene, salicylates, and sulfonamide antibiotics
- Concomitant medications that block the sympathetic nervous system such as beta-blockers

8.5.10 Previous and Concomitant Therapy

Administration of concomitant medications must be reported in the appropriate section of the eCRF, with dosage information, dates of administration, and indication for use. Investigators and site staff should use generic names for concomitant medications if possible. All fields should be completed on the eCRF. See Appendix 3 (Section 17.3) for a list of allowed and prohibited concomitant medications.

8.5.11 Treatment Compliance

Investigators and site staff will review each subject's treatment medication use at scheduled clinic visits and telephone calls, and at any interim clinic visits, and study treatment compliance will be assessed.

8.5.12 Assignment to Treatment

Randomization will be performed through IXRS. The Investigator or designee will access the IXRS to randomize enrolled subjects. The IXRS system will assign a unique randomization number and study medication kit number. Randomization will be stratified by country. No subject may be randomized more than once, and no randomization number will be assigned to more than 1 subject.

8.5.13 Unblinding Procedures

Not applicable for this open-label study.

8.6 Study-Related Devices

8.6.1 Glucometer, Test Strips, and Related Supplies

At the screening visit, each subject will be issued with a glucometer, test strips, and other supplies for use during the study to document hypoglycemic episodes in a prospective manner. The Investigator or qualified site staff will train each subject on the correct use of these supplies and any related procedures, and subjects can obtain additional supplies as needed at subsequent study visits. Subjects will also be issued a Hypoglycemic Events Record in which they will fully record information prospectively about any hypoglycemic events. They will bring this record to each study visit except those brief visits for application of a CGM sensor. Subjects will be allowed to keep the glucometer after the study per local, ethical and legal guidelines and regulations.

8.6.2 FreeStyle Libre Pro Flash Glucose Monitoring System

The FreeStyle Libre Pro Flash Glucose Monitoring System is a glucose-monitoring device indicated for detecting trends and tracking patterns in persons (age 18 and older) with diabetes.

The FreeStyle Libre Pro Flash Glucose Monitoring System aids in understanding the person's glucose profile and detecting episodes of hyperglycemia and hypoglycemia.

Interpretation of the FreeStyle Libre Pro Flash Glucose Monitoring System readings will be based on the trends and patterns analyzed through time using the reports available.

The FreeStyle Libre Pro Flash Glucose Monitoring System consists of a sensor with an applicator, and reader that is used to start the sensor on the subject and gather the glucose data at the end of the CGM period. The sensor has a small, flexible filament that is inserted just under the skin. The sensor can be worn for up to 14 days. Multiple subjects can have their sensor started by the same reader. Once applied, a sensor will measure and store the glucose readings every 15 minutes. Each site will have a single reader that will be used for all their subjects. Readings from the FreeStyle Libre Pro Flash Glucose Monitoring System will not be made available to subjects in real time and so they will continue performing glucose self-testing with the glucometer according to the Investigator's instructions. The FreeStyle Libre Pro Flash Glucose Monitoring System will be used for data collection purposes only and will not be used to make treatment decisions. The system does not require any subject action.

At the screening visit and between 8 and 10 days before the visits at Weeks 12 and 26, subjects will attend a brief visit so the Investigator or designee can apply a CGM sensor to the back of the upper arm according to the instructions in the FreeStyle Libre Pro User Guide. Subjects will also receive a Mealtime & Insulin Dose Record in which they will record the time of meals, and insulin doses for the 8-day CGM period.

Eight days after the screening visit, the subject may remove the sensor and will bring it to the randomization visit; if the end of the 8-day CGM period coincides with the date of the randomization visit, the sensor can be removed at the visit. Subjects will bring both their

Hypoglycemic Events Record and their Mealtime & Insulin Dose Record to the randomization visit.

For the visits at Weeks 12 and 26, the subject will have worn the sensor for the 8-day CGM period before the visit, and the site staff will remove the sensor at the visit. The Investigator or designee will use the reader to retrieve the data from the sensor, and the 8-day Mealtime & Insulin Dose Record will be collected and reviewed. The data from the sensor does not have to be uploaded at the time of the visit, but the Investigator will retain each subject's sensor until it is confirmed the data have been successfully uploaded. Each sensor will be labeled with the subject and visit number and will be stored in a secure location until the end of the study after confirmation of successful upload.

Investigators and staff will review the FreeStyle Libre Pro Flash Glucose Monitoring System warnings and limitations and instruct subjects about the need to avoid medications and conditions that could interfere with the results.

8.7 Primary and Secondary Endpoints

8.7.1 Primary Endpoint

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

8.7.2 Key Secondary Endpoint

- **Efficacy**
  - The change in $HbA1_c$ from baseline at visit Week 26

8.7.3 Other Secondary Endpoints

8.7.3.1 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
- 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

8.7.3.2 Safety

- The incidence and severity of all treatment-emergent adverse events and the following subgroups:
  - Hypoglycemia, which will be fully documented prospectively in the Hypoglycemic Events Record
  - Serious adverse events, including fatal events
  - Adverse events leading to termination of the study treatment and/or early withdrawal from the study
  - IP-related adverse events
  - Injection site reactions
- The incidence of clinically significant laboratory abnormalities
- The incidence of clinically significant abnormalities in ECG and vital signs

8.7.3.3 Efficacy

- 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 $HbA1_c$ of < 7.0% at visit Week 26

8.7.4 Exploratory Endpoints

- Retrospective CGM hypoglycemic rate
- Time in hypoglycemia and hyperglycemia
- Relationship between plasma concentrations of insulin glargine, M1, and M2, and AIA titers

9. STUDY EVALUATIONS BY VISIT

See Section 10 for information about subject assessments.

9.1 Visit 1: Screening: from Day -14 Through Day -1

At the screening visit, subjects will provide informed consent and will be evaluated for eligibility to participate in the study. After the subject signs the ICF, the following information will be collected or procedures performed:

- Eligibility screening
- Adverse events
- Medical history (including diabetes mellitus and thyroid disease history)
- Prior and concomitant medications (including insulin)
- Vital signs, height, body weight, and BMI
- 12-lead ECG
- Physical examination
- Venous blood samples will be collected for the following tests:
    - Routine hematology and chemistry testing including free T4 and TSH (See Section 10.5 for details)
    - FBG test
    - $HbA1_c$
    - AIA (blood should be collected before the subject administers the regular insulin dose)
- Urine samples will be collected for urinalysis and, for women of childbearing potential, a urine pregnancy test
- A capillary blood glucometer, test strips, and other supplies will be issued and the Investigator or designee will provide instruction and conduct training on how to use the glucometer
- The Investigator or designee will apply a CGM sensor and issue an 8-day Mealtime & Insulin Dose Record, and will instruct the subject about the purpose of the CGM, the need to continue performing glucose self-testing with the glucometer, care of the sensor, and how to complete the Mealtime & Insulin Dose Record (subjects will be instructed to bring the record back to their next visit)
- Subjects will also receive a Hypoglycemic Events Record in which they will record information about any hypoglycemic events during their participation in the study
- During the 2-week period between the screening and randomization visits, subjects will have their basal insulin doses optimized as described in Section 8.5.8.

9.2 Visit 2: Randomization (Day 1)

At Visit 2, eligible subjects will be centrally randomized 1:1 in an open-label fashion to receive either Gan & Lee Insulin Glargine Injection or Lantus®. The following information will be collected or procedures performed:

- Concomitant medications and adverse events
- Vital signs, body weight, and BMI
- Venous blood will be collected for the following tests:
  - FBG test
  - Optional PK (blood should be collected before the subject administers the regular insulin dose)
- Urine samples will be collected for urinalysis and, for female subjects of childbearing potential, a urine pregnancy test
- Review of insulin use and glucose results since the previous visit, and the Hypoglycemic Events Record
- The CGM sensor that was applied at the screening visit will be collected (either provided by the subject in a biohazard bag, or removed from arm by the site staff if the end of the 8-day CGM period coincides with the date of the randomization visit)
- The 8-day Mealtime & Insulin Dose Record will be collected and reviewed
- Additional glucose testing supplies will be issued if needed
- IP will be issued
- The Investigator or designee will provide instruction and conduct training on all study procedures and proper dose administration

9.3 Visits 3 and 4: Weeks 2 and 4 (±3 Days)

At each clinic visit, the following information will be collected or procedures performed:

- Concomitant medications and adverse events
- Review of IP and bolus insulin use, glucose results, and the Hypoglycemic Events Record
- Vital signs, body weight, and BMI
- Venous blood will be collected for the following tests:
  - FBG test
  - Optional PK (blood should be collected before the subject administers the regular insulin dose)
- Urine samples will be collected for urinalysis and, for female subjects of childbearing potential, a urine pregnancy test
- IP and other supplies will be issued if needed, and any used insulin kits will be collected for accountability

9.4 Telephone Contacts: Weeks 6, 10, 14, 18, and 22 (± 3 Days)

At these weeks, the Investigator or designee will call the subjects and collect information about concomitant medications, adverse events, use of IP and bolus insulin, and glucose

results. The subject will be asked about any hypoglycemic events and ensure that they have been recorded in the Hypoglycemic Events Record.

9.5 Visit 5: Week 8 (± 3 Days)

At this visit, the following information will be collected or procedures performed:

- Concomitant medications and adverse events
- Review of IP and bolus insulin use, glucose results, and the Hypoglycemic Events Record
- Vital signs, body weight, and BMI
- Venous blood will be collected for the following tests:
  - FBG test
  - $HbA1_c$
  - Optional PK (blood should be collected before the subject administers the regular insulin dose)
- Urine samples will be collected for urinalysis and, for female subjects of childbearing potential, a urine pregnancy test
- IP and other supplies will be issued if needed, and any used insulin kits will be collected for accountability

9.6 Weeks 11 and 25: Brief Visit for CGM Sensor Application

Between 8 and 10 days before the Week 12 and 26 visits, each subject will attend a brief visit during which a new CGM sensor will be applied, and they will also receive a new 8-day Mealtime & Insulin Dose Record in which they will record the time of meals and insulin dosing during the 8-day CGM period.

9.7 Visit 6: Week 12 (± 3 Days)

At this visit, the following information will be collected or procedures performed:

- Concomitant medications and adverse events
- Review of IP and bolus insulin use, glucose results, and the Hypoglycemic Events Record
- Vital signs, body weight, and BMI
- Venous blood will be collected for the following tests:
  - FBG test
  - Routine hematology and chemistry testing including free T4 and TSH
  - AIA and optional PK (blood should be collected before the subject administers the regular insulin dose)
- Urine samples will be collected for urinalysis and, for female subjects of childbearing potential, a urine pregnancy test
- IP and other supplies will be issued if needed, and any used insulin kits will be collected for accountability

- The CGM sensor that was applied at Week 11 will be collected from the subject's arm
- The 8-day Mealtime & Insulin Dose Record will be collected and reviewed

9.8 Visit 7: Week 16 (± 3 Days)

At this visit, the following information will be collected or procedures performed:

- Concomitant medications and adverse events
- Review of IP and bolus insulin use, glucose results, and the Hypoglycemic Events Record
- Vital signs, body weight, and BMI
- Venous blood will be collected for the following tests:
  - FBG test
  - $HbA1_c$
  - Optional PK (blood should be collected before the subject administers the regular insulin dose)
- Urine samples will be collected for urinalysis and, for female subjects of childbearing potential, a urine pregnancy test
- IP and other supplies will be issued if needed, and any used insulin kits will be collected for accountability

9.9 Visit 8: Week 20 (± 3 Days)

At this visit, the following information will be collected or procedures performed:

- Concomitant medications and adverse events
- Review of IP and bolus insulin use, glucose results, and the Hypoglycemic Events Record
- Vital signs, body weight, and BMI
- Venous blood will be collected for the following test:
  - FBG test
  - Optional PK (blood should be collected before the subject administers the regular insulin dose)
- Urine samples will be collected for urinalysis and, for female subjects of childbearing potential, a urine pregnancy test
- IP and other supplies will be issued if needed, and any used insulin kits will be collected for accountability

9.10 Visit 9 (EOT Visit): Week 26 (± 3 Days)

Subjects will visit the study site for the last time at Week 26 of the Treatment Period (Visit 9). The Investigator or designee will perform the following procedures and assessments:

- Concomitant medications and adverse events

- Review of IP and bolus insulin use, glucose results, and the Hypoglycemic Events Record
- The CGM sensor that was applied at Week 25 will be collected from the subject's arm
- The 8-day Mealtime & Insulin Dose Record will be collected and reviewed
- Vital signs, body weight, and BMI
- Venous blood will be collected for the following tests:
  - Routine hematology and chemistry tests, and free T4 and TSH
  - FBG test
  - $HbA1_c$
  - AIA and optional PK (blood should be collected before the subject administers insulin)
- Urine samples will be collected for urinalysis and, for female subjects of childbearing potential, a urine pregnancy test
- 12-lead ECG
- Physical examination
- All remaining IP kits will be collected for accountability
- Any other applicable end-of-treatment procedures will be carried out

9.11 Early Termination Visit

For any subject who is withdrawn before completing all study visits, the Investigator will ensure that the following steps are taken at an early termination (ET) visit:

- Conduct an ET visit performing study activities listed under Visit 9 (Section 9.10) no later than 14 days after withdrawal or discontinuation from the study
- If the subject fails to attend a scheduled ET visit, site staff will make at least 2 attempts to contact the subject via telephone and 2 attempts via written communications delivered by courier (delivery should be confirmed and documented). If the subject does not respond to any of these attempts at communication, he or she will be considered lost to follow-up
- Complete all appropriate eCRF pages, providing the date of and explanation for the subject's withdrawal/discontinuation
- When indicated, the Investigator should arrange for appropriate follow-up medical care for the subjects

If a subject discontinues the study prematurely, it is very important for site personnel to encourage subjects to visit the site at Week 26 (± 4 weeks) (and Week 12 ± 1 week, if applicable) for a blood sample to be obtained for AIA and $HbA1_c$ measurements.

9.12 Follow-up Telephone Call

Site personnel will contact the subjects by phone approximately 30 days after the study completion to collect serious adverse event information.

10. METHODS OF ASSESSMENT

10.1 Pregnancy Testing

Subjects who are pregnant at screening or planning to become pregnant during the study will be excluded from participation in the study. All women of childbearing potential will have a urine pregnancy test at screening and at each clinic visit. Unless a female subject meets at least 1 of the following criteria, she will be considered to be of childbearing potential:

- Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause
- Surgically or congenitally sterile
- Diagnosed as infertile and not undergoing treatment to restore fertility

10.2 Physical Examination

Physical examinations will be performed by a physician or delegate who must be listed on the 1572 as a sub-investigator. This responsibility should be documented on the Site Signature & Duty Delegation Log. The examination will include the following organs or organ systems: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system and nervous system (including a neurological examination; with an assessment of the reflexes, motor and sensory nerve assessment, sensory checks [extremities] and mental status assessment).

The examining physician or delegate completing the physical exam will document an assessment of normal or abnormal for each body system on the Physical Exam source document. Any abnormal finding deemed to be clinically relevant by the Investigator will be reported as an adverse event. See Section 11.1 for more details about reporting adverse events.

10.3 Vital Signs and Body Weight

Systolic blood pressure and diastolic blood pressure will be measured on the same arm (preferentially on the left arm) after the subject has been in a supine/sitting position for 5 minutes. Pulse will be recorded simultaneously with blood pressure measurements.

Body weight (kg) will be measured without shoes or jacket. Height will be recorded at screening to calculate BMI.

During the study, the Investigator may repeat vital signs for safety reasons. Clinically relevant abnormal findings will be reported as adverse events.

10.4 Electrocardiogram

Computerized 12-lead ECG recordings will be obtained, after the subject has been supine for 5 minutes. Each lead will be recorded for at least 3-5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. At a minimum, heart rate, P, PR, QRS, QT and corrected

QT intervals (msec) will be recorded from the 12-lead ECG. A copy of all ECGs will be retained on site and these may be collected for central review if required (i.e., in case emerging ECG data necessitate expert evaluation).

For the purposes of screening, the Investigator or a designee will evaluate whether the ECG is normal or abnormal, and if abnormal, whether the abnormality will exclude the subject from participating in the study.

Investigators may repeat ECGs for quality or safety reasons. Any abnormal finding deemed to be clinically relevant by the Investigator will be reported as an adverse event. Subjects with clinically relevant cardiovascular side effects or adverse events, or clinically relevant ECG changes must be withdrawn from the study (see Section 8.4.3).

10.5 Clinical Laboratory Testing

The following routine clinical laboratory tests will be performed as indicated in Table 1 and Section 9.

- Complete blood count (red blood cell [RBC] count, white blood cell [WBC] count, hemoglobin, hematocrit, platelet count, RBC indices, and a 5-part WBC differential [percentages of neutrophils, lymphocytes, monocytes, eosinophils, and basophils])
- Chemistry metabolic panel, including glucose, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium, total protein, total and conjugated bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and creatine kinase
- Serum lipid panel including total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides
- TSH and free T4

The following additional blood tests will be performed at specific visits as outlined in Table 1 and Section 9. More information about sample collection and handling will be included in the respective laboratory manuals.

- AIA (blood should be collected before the subject administers insulin)
- Optional PK for a subset of subjects who consent to the additional testing (insulin glargine, M1, and M2 concentrations; blood should be collected before the subject administers insulin)
- FBG test (venous)
- $HbA1_c$

10.6 Urinalysis

Urinalysis, including glucose, protein, and ketones, will be performed at each study visit in the clinic.

11. SAFETY MEASUREMENTS AND VARIABLES

11.1 Adverse Events

The definitions and reporting procedures provided in this protocol comply with the current CFR 21 Part 312. An adverse event is any untoward medical occurrence or worsening of a pre-existing condition, regardless of the relationship to the investigational medicinal product. An adverse event can therefore be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the use of an investigational medicinal product whether or not considered related to the investigational medicinal product.

Adverse events will be recorded beginning at the screening visit. Nonserious adverse events will be recorded from the time informed consent is signed through the subject's last study visit (or termination if the subject terminates early from the study for any reason). Serious adverse events will be collected from the time informed consent is signed through and including 30 calendar days after the last dose of treatment with IP.

The Investigator or designee will record all adverse events on the eCRF, regardless of the Investigator's assessment of causality, including a description of the event, severity, time of occurrence, duration, any action (e.g., treatment and follow-up tests), the event outcome, and the Investigator's assessment of the relationship to the study treatment.

11.2 Serious Adverse Events

A serious adverse event is any untoward medical occurrence or effect that meets any of the following criteria:

- results in death
- is life-threatening (refers to events during which a subject was actually at risk of death, and not to events that might have become life-threatening if they had occurred in a more severe form or if the subject had not received treatment)
- requires hospitalization or causes prolongation of existing inpatient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital abnormality/birth defect in the offspring of a study subject
- is an important medical event that does not meet any of the above criteria but may require medical intervention to prevent the outcomes listed above, or is considered important by the Investigator; examples of important medical events include:
    - Bronchospasm requiring treatment in the emergency department or at home
    - Development of a blood dyscrasia
    - Diagnosis of a substance use disorder

11.3 Adverse Events of Special Interest

An adverse event of special interest is a noteworthy serious or nonserious event that a sponsor may want to carefully monitor because it might be a potential precursor or prodrome for a more serious condition in susceptible individuals. In this study, hypoglycemia will be monitored as an adverse event of special interest. When an adverse event of hypoglycemia is entered into the electronic data capture system, the system will prompt the user to provide additional information.

11.4 Reporting of Serious Adverse Events to PRA

In addition to completing all eCRFs related to serious adverse events, the Investigator or designee must report all serious adverse events to PRA Drug Safety within 24 hours after learning about the event, even if the information is incomplete.

PRA Drug Safety Contact Information:

Europe:

PRA Health Sciences - Mannheim, Germany
Drug Safety Helpline: +49 621 878 2154
Fax: +44 1792 525 720
E-mail: MHGSafety@prahs.com

Americas:

PRA Health Sciences – Charlottesville, VA, USA
Drug Safety Helpline: 1-800-772-2215 or 1-434-951-3489
Fax: 1-888-772-6919 or 1-434-951-3482
E-mail: CHOSafety@prahs.com

To be valid, the initial serious adverse event report must include the following minimal data:

- A reporting source (the Investigator's name and/or site number, and contact information)
- A subject identifier
- The identity of IP
- A serious adverse event term, description, or outcome

Investigators will provide the following additional data as soon as possible, but these data are not required for the initial report if they are not immediately available:

- Event start date
- Event end date if known; the end date is the date on which serious criteria were no longer met; i.e., the event was no longer serious
- Severity (Grades 1, 2, 3, 4, or 5 according to the Common Terminology Criteria for Adverse Events [CTCAE] version 4.03)
- The Investigator's assessment of causality (unrelated, unlikely related, possibly related, probably related, or definitely related)
- Any serious criteria that apply to the event (see Section 11.2)

Investigators will submit follow-up reports for serious adverse events whenever additional pertinent information becomes available and will provide copies of all pertinent documents such as hospital records, admission and discharge summaries, surgical records, laboratory reports, autopsy reports, and other documents when requested and applicable. Monitoring of Subjects with Adverse Events.

11.5 Monitoring of Subjects with Adverse Events

Each subject must be carefully monitored for adverse events, including clinically significant abnormal laboratory test results, physical examination findings, and ECG results. At each study visit or communication, the Investigator or designee will ask subjects about any new symptoms or worsening of baseline symptoms that could indicate an adverse event.

11.5.1 Abnormal Laboratory Test Results

Changes or abnormalities in clinical laboratory results judged to be clinically significant by the Investigator will be recorded as adverse events. If an unexplained abnormal laboratory test result occurs, the Investigator or designee will promptly repeat the test and monitor the subject until the result has returned to the normal range or an adequate explanation of the abnormality is found.

11.5.2 Abnormal Physical Examination Findings or ECG Changes

Changes or abnormalities in physical examination findings or ECGs judged to be clinically significant by the Investigator will be recorded as adverse events.

11.6 Overdose of Study Medication

Any overdose of the study medication, with or without associated adverse events, must be reported to PRA Drug Safety. Overdose will be reported in the eCRF. All reports of overdoses must be filed in the Study Center File. Any adverse event associated with the overdose will be reported on relevant adverse event/serious adverse event sections in the eCRF.

Investigators will instruct subjects how to manage the dose of their study medication and other medications for diabetes, and procedures to be followed if an overdose occurs. Subjects will be instructed to seek medical assistance immediately if they experience an overdose of study medication and to notify the Investigator as soon as feasible.

11.7 Pregnancy

Pregnancy itself is not regarded as an adverse event unless the Investigator suspects an IP may have interfered with the effectiveness of a contraceptive medication. However, any

pregnancy during the study and the outcome of the pregnancy (spontaneous miscarriage, elective termination, normal birth or congenital anomaly) must be reported to PRA.

If a subject becomes pregnant during the study, she will discontinue IP immediately and report the pregnancy to the Investigator. The subject will attend an end-of-treatment visit and should be followed by the Investigator through childbirth or termination of the pregnancy. The Investigator will submit an initial report upon learning of the pregnancy, and a follow-up form when the outcome of the pregnancy is known. If the female partner of a male subject becomes pregnant, the subject may continue in the study, but the pregnancy should be reported in the same manner as described above. Any congenital anomaly or birth defect in the offspring of the subject will be reported as a serious adverse event. Investigators should contact the Medical Monitor if questions arise.

12. DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by PRA Health Sciences.

12.1 Data Management

An electronic clinical database (Medidata Solutions) will be used and a Data Management Plan will be prepared by PRA Health Sciences.

Previous and concomitant medications will be coded using the latest available WHO Drug Reference Dictionary. Coexistent diseases and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can be made only by written agreement between Gan & Lee Pharmaceuticals USA and PRA Health Sciences.

12.2 Sample Size Estimation

Enrollment is planned for 550 subjects overall (275 subjects per treatment group). The primary analysis for immunogenicity will be an equivalence test using the 2 one-sided tests (TOST) approach with α=0.05. This sample size was chosen to achieve over 80% power on the equivalence test of proportion of subjects under the margins dependent on the observed treatment-induced AIA rate. For example, a sample size of 550 will provide approximately 85% power on the equivalence test of proportion of subjects with treatment-induced AIA using an event rate of 30% and a margin of 12% (Table 4). 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. For this sample size of 550, no drop outs are considered in the calculation. Subjects will be encouraged to come back for assessments even if they have discontinued treatment early.

The 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 4. Linear interpolation will be used for values between AIA rates in the table.

Table 4: 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%

AIA = anti-insulin antibodies.

Sample size calculations were performed using EAST Version 6.4.

12.3 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Table, listing, and figures shells will also be provided.

12.4 Randomization

Subjects will be randomized in a 1:1 ratio to Gan & Lee Insulin Glargine Injection or Lantus® treatment. Subject randomization will be stratified by country.

Registration and randomization will take place using a centralized 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 report forms.

The study is 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 (hereafter referred to as the Blinding Plan).

12.5 Analysis Sets

12.5.1 Safety Analysis Set

The Safety Analysis Set is composed of all randomized subjects who receive any IP, even a partial dose (Gan & Lee Insulin Glargine Injection or Lantus®). Subjects in the Safety Analysis Set will be grouped according to the treatment they actually received. All safety and immunogenicity endpoints will be analyzed using the Safety Analysis Set.

12.5.2 Full Analysis Set

The Full Analysis Set (FAS) is composed of all randomized subjects. Subjects in the FAS will be grouped according to planned treatment. All efficacy endpoints will be analyzed using the FAS based on the subject's randomized treatment.

12.5.3 Per Protocol Set

The Per Protocol (PP) Analysis Set is composed of all randomized subjects who received at least 1 partial dose and do not have any important protocol deviations during the first 26 weeks of the study. Subjects in the PP Analysis Set will be grouped according to actual treatment received. The PP Analysis Set will be used for sensitivity analyses of confirmed positive AIA and HbA1c and demography summary.

12.5.4 PK Analysis Set

The PK Analysis Set is composed of all randomized subjects who receive at least 1 partial dose and provide at least 1 pre-dose assessment that is sufficient to derive plasma concentration of insulin glargine, M1, or M2. Subjects in the PK analysis set will be grouped according to the treatment they actually received.

12.6 Statistical Methods

In general, categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the number of observations (n), mean, and standard deviation, median, minimum 25th and 75th percentiles, and maximum. All summaries will be presented by treatment groups as well as the total. All statistical analyses will be performed using SAS®. The SAS® version number will be noted in the SAP.

12.6.1 Missing Data

Missing data will be imputed for the primary immunogenicity analysis in the manner shown in Table 5.

Table 5: Imputation Rules for Missing Data in the Primary Immunogenicity Analysis

	Baseline[a]	Visit Week 12	Visit Week 26	Result/Imputation Rule
1.	x	x	x	No imputation.
2.	x	x	o	Subject will be counted as developing a treatment-induced AIA, impute visit Week 26 as positive result
3.	x	o	x	Subject will be counted as developing a treatment-induced AIA, impute visit Week 12 as positive result
4.	x	o	o	Subject will be counted as developing a treatment-induced AIA, impute visit Week 12 and visit Week 26 as positive result
5.	o	x	x	Subject will be counted as developing a treatment-induced AIA if visit Week 12, visit Week 26, or unscheduled assays up to visit Week 26 indicate positive result; otherwise, subject will be counted as not developing a treatment-induced AIA (all assays up to visit Week 26 are negative).
6.	o	x	o	Subject will be counted as developing a treatment-induced AIA, impute visit Week 26 as positive result
7.	o	o	x	Subject will be counted as developing a treatment-induced AIA, impute visit Week 12 as positive result
8.	o	o	o	Subject will be counted as developing a treatment-induced AIA, impute visit Week 12 and visit Week 26 as positive result

AIA = anti-insulin antibodies; o = AIA data missing, x = AIA data not missing.
[a] No imputation will be performed for missing baseline values.

Additional sensitivity analyses on the imputation, which explore the limitation(s) of the data or assumption(s) of the primary analysis being evaluated in each sensitivity analysis and how the analysis addresses each, will also be discussed in the SAP.

Missing data will be imputed for the $HbA1_c$ analysis. The robustness of the imputation will be explored via sensitivity analyses using multiple imputation and including a tipping point analysis. Full details of the multiple imputation procedure will be presented in the SAP.

12.6.2 Demographic and Baseline Data

Demographic information and baseline characteristics will be summarized for the FAS, Safety Analysis Set, and PP Set. Descriptive statistics will be provided for age, sex, race, ethnicity, baseline body weight, height, and BMI.

Medical history conditions will be coded using most current version of MedDRA at time of database lock. The number and percentage of subjects with each medical history term will be summarized by MedDRA system organ class and preferred term.

12.6.3 Subject Disposition

The number and percentage of subjects screened, randomized and treated in the study will be presented, together with the number and percentage of subjects who withdrew from the study prematurely, with a breakdown of the corresponding reasons for withdrawal.

A tabulation of the number and percentage of subjects randomized in each country and center will be presented.

12.7 Primary Endpoint

12.7.1 Incidence of Treatment-Induced Anti-Insulin Antibodies

The primary analysis for immunogenicity will be an equivalence test using the TOST approach with α=0.05 which is algebraically equivalent to comparing the limits of the 90% confidence interval (CI) for treatment-induced AIA development via a test of difference in proportions based on normal approximation (-margin, +margin) where the margin is dependent on the observed treatment-induced AIA rate in Lantus® and is defined in Table 4. The estimand of interest for the primary immunogenicity analysis is the difference in treatment-induced immunogenicity 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 [17]).

Sensitivity analyses including worst-case imputation and using a ‘Composite Strategy’ will be conducted.

12.8 Key Secondary Endpoint

12.8.1 Change from Baseline in $HbA1_c$ at 26 Weeks

The key secondary analysis will be to evaluate equivalence (FDA)/noninferiority(EMA) of Gan & Lee Insulin Glargine Injection relative to Lantus® for $HbA1_c$ by comparing the 90% confidence interval with (-0.4%, 0.4%) for equivalence using the TOST approach and by comparing the upper limit of the 95% CI with 0.4% for noninferiority from a pattern mixture model that uses multiple imputation analyzed using Analysis of Covariance (ANCOVA) with treatment and stratification factor of country included as fixed effects and baseline $HbA1_c$ included as a covariate. Separately in each treatment group, the imputation will use the outcomes of patients who completed the study (including subjects who discontinued treatment but provided a visit Week 26 HbA1c sample) to impute outcomes in patients without actual visit Week 26 recorded results under the missing at random assumption. Full details of the multiple imputation procedure will be specified in the SAP. Analysis of $HbA1_c$ will follow a hierarchical testing strategy: first, equivalence/noninferiority will be tested with a margin of 0.4%; secondly, if and only if the test using a margin of 0.4% is significant, then equivalence will be tested using a margin of 0.3%. Analyses of $HbA1_c$ in the testing hierarchy will be conducted on the Full Analysis Set consisting of all randomized subjects according to randomized treatment with supportive analyses on the Per Protocol Analysis Set. A tipping point analysis with varying assumptions about the differences on each treatment arm between outcomes in patients who withdrew from the study early and outcomes in patients who completed the study will be performed. The estimand of interest for the $HbA1_c$ analysis is the difference in change from baseline for HbA1c using the "treatment policy strategy".

12.9 Other Secondary Endpoints

12.9.1 Immunogenicity

12.9.1.1 Subjects with Negative Anti-Insulin Antibodies at Baseline Who Develop Confirmed Anti-Insulin Antibodies

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 will be compared using a normal test of difference in proportions.

12.9.1.2 Subjects with a 4-fold Increase in Titers

The percentage of subjects in each treatment group with confirmed positive AIA at baseline who have at least a 4-fold increase in titers after baseline and up to visit Week 26 will be compared using an exact test of difference in proportions.

12.9.1.3 Change in Anti-Insulin Antibody Titer

The mean change from baseline in each treatment group in AIA titers at visit Week 12 and visit Week 26 will be summarized descriptively in subjects with confirmed positive AIA at baseline.

12.9.1.4 Subjects with Confirmed Anti-Insulin Antibodies Who Develop Anti-Insulin Neutralizing Antibodies

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 will be compared using an exact test of difference in proportions.

12.9.1.5 Subjects who Develop Confirmed 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 a normal test of difference in proportions.

12.9.2 Safety

All reported adverse events will be assigned a system organ class and preferred term according to MedDRA and graded according to CTCAE version 4.03. The number and percentage of subjects with treatment-emergent adverse events (all adverse events, hypoglycemia, serious adverse events [including fatal events], adverse events leading to termination of the study treatment and/or early withdrawal from the study, and IP-related adverse events, and injection site reactions) will be presented. Vital signs, body weight and BMI, ECG, and laboratory parameters will be summarized by treatment and visit.

12.9.3 Efficacy

12.9.3.1 Proportion of Subjects Achieving Glycemic Control

The following secondary efficacy variables will be analyzed using a test of difference of proportions based on the normal approximation and confidence intervals:

- 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 $HbA1_c$ of < 7.0% at visit Week 26

12.10 Exploratory Variables

The retrospective CGM hypoglycemic rate and time in hypoglycemia and hyperglycemia will be summarized for subjects in the Safety Analysis Set. The plasma concentrations of insulin glargine, M1, and M2 will be plotted against AIA titers.

12.11 Data Safety Monitoring Board

A Data Safety Monitoring Board is not planned unless determined to be clinically indicated.

13. MONITORING PROCEDURES (QUALITY ASSURANCE)

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. To fulfill these obligations and to stay apprised of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of adverse events. The Investigator must provide the monitor with full access to all source and study documents.

13.1 Risk and Quality Tolerance Limits and Routine Monitoring

Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRFs, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the start of the study.

The Sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the clinical study report.

13.2 Inspections and Auditing Procedures

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the investigative site during or after the study. The Investigator or designee should contact the Sponsor/contract research organization (CRO) immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

14. STUDY MANAGEMENT AND MATERIALS

14.1 Electronic Case Report Forms

Electronic CRFs will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRFs must be reviewed, electronically signed, and dated by the Investigator.

Access to eCRFs will be strictly password-protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by the examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

14.2 Data Collection

During each study visit or telephone contact, the Investigator or designee will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes will contain:

- The date of the visit and the corresponding week or visit number in the study schedule
- The subject's general condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported adverse event, and the Investigator's assessment as to whether or not the reported event is IP-related
- Changes in concomitant medications or dosages
- A general reference to the procedures completed
- The signature or initials of all physicians and other qualified medical designees making an entry in the medical record (or electronic equivalent)

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record as described above.

14.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed ICF for each subject shall be filed with records kept by the Investigator and a copy shall be given to the subject.

14.4 Record Maintenance

All data derived from the study will remain the property of Gan & Lee Pharmaceuticals.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs and IP inventory must be kept on file.

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of IPs. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and regulatory authorities.

If an Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

14.5 Confidentiality

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each subject's anonymity is maintained. On eCRFs and other documents submitted to the Sponsor or the CRO, subjects must not be identified by name. Instead, subjects will be known only by the unique subject number allocated to them

to ensure confidentiality on all study documentation. The Investigator will keep a separate log of these codes.

To comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the health authorities to review subjects' medical records as they relate to this study. Only the subject's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor or the CRO (e.g., consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site and subject identity will remain confidential in all publications related to the study.

15. ADMINISTRATION PROCEDURES

15.1 Regulatory Approval

Gan & Lee Pharmaceuticals USA or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No subject may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the Investigator and to the IRB(s)/IEC(s).

15.2 Protocol Amendments

In accordance with ICH E6 Guideline for GCP the Investigator should not implement any deviation from, or changes to the protocol without agreement by the Sponsor and documented approval from the IRB/IECs of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB/IECs assuming this responsibility. The Investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects. In these cases, the IRB/IEC must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB/IEC, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written ICF will require modification. The modified ICF must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from subjects enrolled in the study before participation continues.

15.3 Protocol Adherence and Deviations

The Investigators and all staff involved with the study must read the protocol thoroughly and follow the instructions contained in it. However, exceptions will be made in emergency situations when the protection, safety, or well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a Sub-Investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

15.4 Publication Policy

After completion of the study, the Investigator(s) may prepare a joint publication with the Sponsor. The Investigator(s) must undertake not to submit any part of the data from this protocol for publication without the prior consent of Gan & Lee Pharmaceuticals USA.

15.5 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated. The Sponsor will provide each Investigator with a copy of the final report for retention.

15.6 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

15.7 Insurance, Indemnity and Compensation

Gan & Lee Pharmaceuticals USA undertakes to maintain an appropriate clinical study insurance policy.

Deviations from the study protocol - especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer

treatment periods - are not permitted and shall not be covered by the statutory subject insurance scheme.

15.8 Discontinuation of the Study

This study may be terminated by the Sponsor. Reasons for discontinuation of the study may include the following situations:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Discontinuation of study drug development

The study may also be terminated prematurely if both the Investigators and the Sponsor agree such action is in the best interests of subjects and is justified on either medical or ethical grounds. Should early termination be necessary, subjects should stop taking the study medication immediately. Every documented effort should be made by the Investigator to ensure that the subject returns to the site as soon as possible to complete one final EOT visit. In terminating the study, Gan & Lee Pharmaceuticals USA, PRA, and the Investigators will ensure that adequate consideration is given to the protection of the subjects' interests.

The Investigator or the Sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

15.9 Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained in accordance with GCP standards.

16. REFERENCE LIST

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16. Guidance for Industry and Food and Drug Administration Staff. Collection of Race and Ethnicity Data in Clinical. October 26, 2016. FDA website. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126396. Accessed January 6, 2017.

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17 APPENDICES

17.1 Appendix 1: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into

consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of

interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics

committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2 Appendix 2: Elements of Informed Consent

ELEMENTS OF INFORMED CONSENT

Both the informed consent discussion and the written ICF and any other written information to be provided to subjects should include explanations of the following:

- That the study involves research.
- The purpose of the study.
- The study treatment(s) and the probability for random assignment to each treatment.
- The study procedures to be followed including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the study that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of study-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.

- The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The expected duration of the subject's participation in the study.
- The approximate number of subjects involved in the study.

17.3 Appendix 3: Allowed and Prohibited Concomitant Medications

These medication lists are not comprehensive. Please contact your Clinical Research Associate if you have questions about medications not listed here.

Allowed Medications	
Basal Insulins Allowed at Study Entry[a]	**Other:**
Lantus® (insulin glargine)	Metformin®
Toujeo® (insulin glargine)	Topamax® (topiramate)[b]
Soliqua® (insulin glargine and lixisenatide)	Cycloset® (bromocriptine mesylate)[b]
Tresiba® (insulin degludec)	
Levemir® (insulin detemir [rDNA origin])	
Neutral protamine Hagedorn	

[a] Subjects will replace their previous basal insulin with the investigational product for the duration of the study.
[b]Topamax® and Cycloset® are allowed only if NOT used for obesity. The approved indications for Topamax® are headache, seizures, and neuropathy; the approved indication for Cycloset® is diabetes.

Prohibited Medications	
Biosimilars	**Obesity Medications**
Mylan/Biocon – glargine	Phentermine
Pfizer – glargine	Belviq® (lorcaserin)
Merck – glargine	Contrave® (naltrexone/bupropion)
Eli Lilly – Basaglar® (glargine)	Saxenda® (liraglutide 3.0 mg daily dose)
Sanofi - lispro	Qysmia® (phentermine and topiramate extended-release)
	Alli® (orlistat; available over-the-counter)
GLP1-R Agonists	
Bydureon® (exenatide long-acting)	**SGLT2i**
Byetta® (exenatide)	Jardiance® (empagliflozin)
Trulicity® (dulaglutide)	Farxiga® (dapagliflozin)
Tanzeum® (albiglutide)	Invokana® (canagliflozin)
Victoza® (liraglutide; up to 1.8 mg/day)	
Lyxumia® (lixisenatide)	**DPP4i**
Ozempic® (semaglutide)	Januvia® (sitagliptin)
	Nesina® (alogliptin)
	Onglyza® (saxagliptin)
Other	
Newly-prescribed or high-dose corticosteroids (chronically administered oral, inhaled, topical, or intra-articular corticosteroids at a stable dose are allowed if no increase in dose is anticipated during the study)	
Immunosuppressants or immune response-modifying drugs	
Cytostatic agents	
Any medication intended to cause weight loss or weight gain	

DPP4i = dipeptidyl peptidase 4 inhibitor; GLP1-R = glucagon-like peptide 1 receptor; SGLT2i = sodium glucose cotransporter-2 inhibitor

The use of pre-exposure prophylactic (PREP) HIV medications must be reviewed with the Medical Monitor.