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Immunogenicity, efficacy, and safety of biosimilar insulin glargine (Gan & Lee glargine) compared with originator insulin glargine (Lantus®) in patients with type 2 diabetes after 26 weeks' treatment: A randomized open label study

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Abstract

Aim: To evaluate the equivalence of immunogenicity, safety and efficacy of Gan & Lee (GL) Glargine (Basalin®; Gan & Lee Pharmaceutical) with that of the reference product (Lantus®) in adult participants with type 2 diabetes mellitus.

Methods: This was a phase 3, multicenter, open-label, equivalence trial conducted across 57 sites. In total, 567 participants with type 2 diabetes mellitus were randomized in a 1:1 ratio to undergo treatment with either GL Glargine or Lantus® for 26 weeks. The primary endpoint was the proportion of participants in each treatment arm who manifested treatment-induced anti-insulin antibodies (AIA). Secondary endpoints included efficacy and safety metrics, changes in glycated haemoglobin levels, and a comparative assessment of adverse events. Results were analysed using an equivalence test comparing the limits of the 90% confidence interval (CI) for treatment-induced AIA development to the prespecified margins.

Results: The percentages of participants positive for treatment-induced glycated haemoglobin by week 26 were similar between the GL Glargine (19.2%) and Lantus® (21.3%) treatment groups, with a treatment difference of −2.1 percentage points and a 90% CI (−7.6%, 3.5%) (predefined similarity margins: −10.7%, 10.7%). The difference in glycated haemoglobin was −0.08% (90% CI, −0.23, 0.06). The overall percentage of participants with any treatment-emergent adverse events was similar between the GL Glargine (80.1%) and Lantus® (81.6%) treatment groups.

Conclusions: GL Glargine was similar to Lantus® in terms of immunogenicity, efficacy, and safety, based on the current study.

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biosimilar, immunogenicity, insulin glargine, type 2 diabetes mellitus

1 | INTRODUCTION

Diabetes mellitus (DM) is a chronic, progressive disease with significant health consequences.[1,2] Type 2 diabetes mellitus (T2DM) is notable for its insulin resistance, often necessitating insulin therapy as β-cell function declines. Insulin treatment is crucial for managing type 1 diabetes mellitus (T1DM) and advanced T2DM, aiming to reduce hyperglycaemia and optimize glycated haemoglobin (HbA1c).[3–5] Exogenous insulins, including basal and bolus insulins, mimic natural insulin secretion patterns, achieving optimal glycaemic control and preventing complications.[6] Basal insulin provides a steady, continuous level of insulin to control basal blood glucose levels between meals and overnight.[7] Recent biomolecular advancements have produced stable basal insulin options such as insulin glargine, insulin degludec, and insulin detemir.[8,9]

Advancing insulin technology often creates access issues in socioeconomically deprived areas of the world, particularly in low- to middle-income regions.[10–12] As a result, many patients may be deprived of the potential therapeutic benefits of these advanced insulin analogues, underscoring the need for strategies to enhance their availability and reduce the medical costs of managing diabetes and related complications.[13] Fortunately, the emergence of biosimilar insulins offers a prospective path to reducing treatment expenses compared with the original insulin products while ensuring comparable efficacy and safety profiles.[14,15] The introduction of these biosimilars aims to alleviate the financial burden on both patients and health care systems while maintaining therapeutic efficacy and safety.[16] Several biosimilar insulins have been launched on the market in the past decade, such as Basaglar® and Semglee®, with more biosimilar insulins in development.[17]

Lantus® (Insulin glargine), the dominant branded basal insulin analogue, received regulatory approval from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2000 as a once-daily subcutaneous treatment for both T1DM and T2DM.[18,19] Insulin glargine has a longer duration of action than human insulin because of specific modifications.[9,20] These modifications enhance the stability of the insulin molecule, resulting in delayed and prolonged absorption following a subcutaneous injection.[21] The global insulin glargine market was valued at US$ 6153.5 million in 2021, which represents half of the global basal insulin market share, and is forecast to reach a value of US$ 6257.7 million by 2028.[22]

The insulin glargine of Gan & Lee Pharmaceutical, branded as Basalin®, was successfully launched in China in 2005.[23] Since its launch, Basalin® has experienced consistent growth in sales. By the third quarter of 2022, domestic sales of Basalin® reached 11.6 million units, which constitutes approximately 33.5% of China's insulin glargine market share.[24] In alignment with the global initiative to augment the accessibility and affordability of basal insulin therapy, Basalin® is being pursued as a proposed biosimilar to Lantus® outside of China. On a global scale, Gan & Lee's insulin glargine (GL glargine) has secured approval in 19 countries. Notably, these approvals exclude the United States (US) and European Union (EU) regions with nearly a quarter of the worldwide adult diabetic population.[25] To commercialize GL glargine in the US and EU, a phase 1 pharmacokinetic (PK) and pharmacodynamic (PD) bioequivalence study was conducted. GL Glargine and Lantus® showed comparable PK, PD, and safety characteristics in patients with T1DM in this phase 1 euglycaemic clamp trial.[26] Two phase 3 immunogenicity studies of this proposed biosimilar insulin were set up according to the requirements of US and EU regulations in 2017, although large phase 3 studies can currently be waived by both the FDA and EMA when referring to the updated guidelines issued in 2019.[27] This phase 3 multicenter, open-label equivalence study was conducted to compare the immunogenicity, safety, and efficacy of GL Glargine with the reference product Lantus® in patients with T2DM.

2 | METHODS

2.1 | Objectives

The primary objective of this 26-week study was to assess the equivalence of GL Glargine and Lantus® in terms of immunogenicity among

individuals diagnosed with T2DM. The primary endpoint of this study was the percentage of participants in each treatment group who developed treatment-induced AIA, defined as newly confirmed positive AIA (negative AIA status at baseline but positive for AIA at week 26) or an important (at least a four-fold) increase in titer after baseline and up to visit week 26. The secondary objectives were to evaluate the percentage of participants who had newly confirmed positive AIA or an important increase in titers after baseline and up to visit week 26 and to evaluate the safety and efficacy of GL Glargine in comparison with Lantus®.

2.2 | Study design

This was a multicenter, open-label, randomized, phase 3, 26-week study. Before the initiation of the study, the research protocol underwent a submission process to the Independent Ethics Committee or Institutional Review Board, adhering to relevant national or local regulations. Any amendments made to the protocol were also submitted for review and approval, and the study was registered at ClinicalTrials.gov (NCT03371108). Written informed consent was obtained from all participants, and the study was conducted in full accordance with the International Council for Harmonization for Good Clinical Practice and the Declaration of Helsinki.

The main inclusion and exclusion criteria are listed in the Supplementary materials. Eligible participants who met the inclusion criteria and none of the exclusion criteria were randomized 1:1 using the Interactive Web Response System (IWRS) to receive either GL Glargine or Lantus® for 26 weeks (Figure 1). No stratification was applied in this study. GL Glargine was administered as a subcutaneous injection using Gan & Lee UnoPen injection pens (prefilled glass cartridge), and Lantus® was administered using SoloStar® prefilled pens.

Participants who were already using insulin at the time of enrolment were required to continue their oral antidiabetic medications (OAMs) and substitute their basal insulin with the investigational product (IP). Participants who were not using basal insulin at enrolment continued their OAMs, added the IP and adjusted insulin dosing individually according to the metabolic status of the participant and at the discretion of the clinical investigational team at the site. All participants underwent optimization and adjustments of insulin dosing as well as OAM dosing as necessary (Table S1). Throughout the study, participants in both treatment groups were evaluated through a 2-week screening visit, a 26-week randomization visit, and a 30-day follow-up visit.

2.3 | Assessments

The assessment of immunogenicity followed a comprehensive one-assay and tiered approach.[28,29] Serum samples obtained at various time points (baseline, week 12 and week 26) from both treatment groups underwent analysis using the fully validated electrochemiluminescence bridging assay. This assay was utilized to detect and confirm the presence of binding AIA in human serum, employing a screening and confirmatory assay known as the Method Validation for Glargine ADA. Furthermore, for samples that tested positive in the confirmatory assay, the antibody titre and the presence of neutralizing antibodies (NAbs) were determined using Method Validation for Glargine NAb.[30] More details were described in Supplementary materials. Venous blood samples were collected to evaluate glycaemic control by measuring levels of HbA1c and fasting blood glucose (FBG). All samples were processed and analyzed at a central laboratory facility. Safety assessments included the incidence and severity of all treatment-emergent adverse events (TEAEs), incidence of clinically significant laboratory abnormalities, and incidence of clinically significant abnormalities in electrocardiograms and vital signs. In addition, continuous glucose monitoring data were collected for the rate of hypoglycaemia.

2.4 | Statistical analysis

The safety and immunogenicity analyses were conducted using the safety analysis set, which included all randomized participants who received any IP. These analyses were performed based on the actual treatment received by each participant. The efficacy analyses, on the other hand, were carried out using the full analysis set, which included all randomized participants and was based on the treatment originally assigned. In general, categorical variables were summarized using counts and percentages. Continuous variables were summarized using the number of observations, mean, SD, median, minimum, 25^{th} and 75^{th} percentiles, and maximum. All statistical analyses were performed using SAS® (SAS version 9.4).

For the primary immunogenicity endpoint analysis, an equivalence test was conducted by comparing the limits of the 90% confidence interval (CI) for the development of treatment-induced AIA to prespecified margins (−10.7%, 10.7%). These margins were determined based on the unadjusted rate of treatment-induced AIA in the Lantus® group. Equivalence was considered to be shown if the entire 90% CI fell within the predefined similarity margins. A logistic regression model was used to evaluate the number and percentage of participants in each treatment group who developed treatment-induced AIA by week 26, estimating the difference in proportions along with the corresponding 90% CI. The primary analysis focused on treatment-induced AIA rates regardless of whether all participants tolerated or adhered to the study treatment or received other insulin treatments and used a data imputation method that generally assumed a positive treatment-induced AIA result for missing data (Table S2). Subgroup analyses and sensitivity analyses were conducted, including sensitivity analyses for participants who had no missing data and had completed treatment. The hypoglycaemia event rate (based on Investigator CTCAE) was compared between treatment groups using a negative binomial regression model. Additional statistical methods were described in more detail in the Supplementary materials.

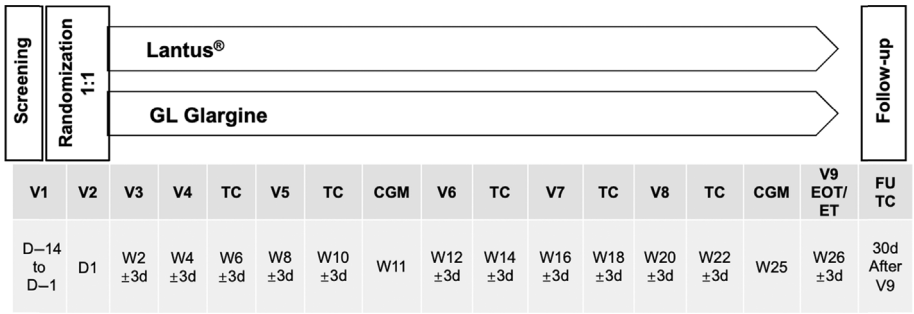

FIGURE 1 Flow diagram of study GL-glargine. In weeks 11 and 25, participants attended a brief visit for the application of a CGM sensor. CGM, continuous glucose monitoring; d/D, day/Day; EOT, end of treatment; ET, early termination; FU, follow-up; GL Glargine, Gan & Lee insulin glargine injection; Lantus®, European Union-approved Lantus; N, number of participants; TC, telephone call; V, visit; W, week.

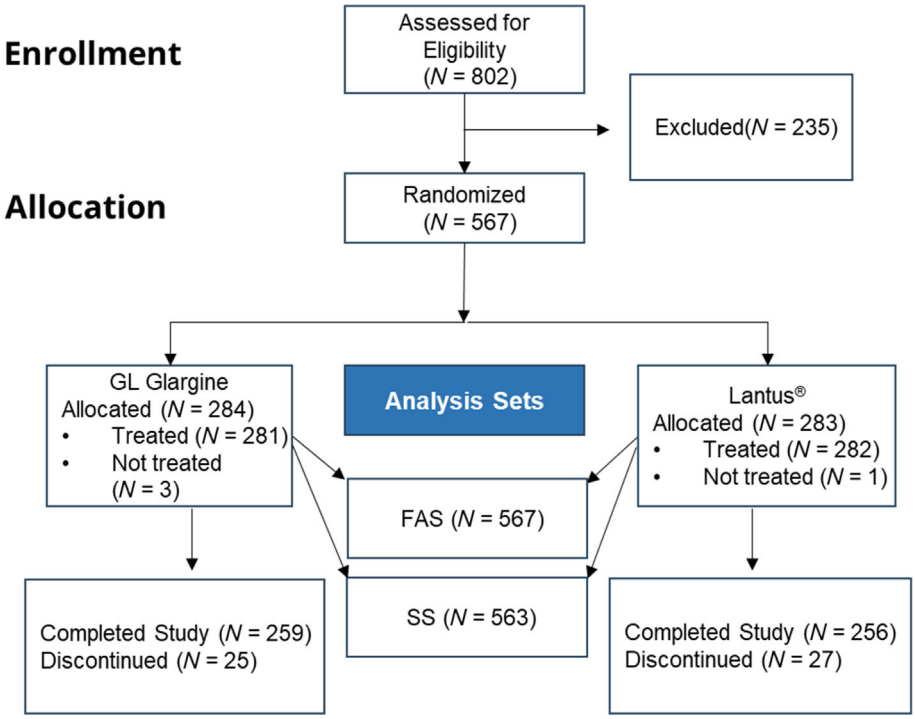

FIGURE 2 Disposition and analysis sets. FAS, full analysis set; GL Glargine, Gan & Lee insulin glargine injection; Lantus®, European Union-approved Lantus; N, number of participants; SS, safety analysis set.

3 | RESULTS

3.1 | Disposition, demographic, and baseline characteristics

All participants included in the study met the diagnostic criteria for T2DM. In total, 802 participants were screened, and 567 participants (70.7%) were randomly assigned (GL Glargine, N = 284; Lantus®, N = 283). In total, 515 participants (90.8%) completed the study, with similar percentages of participants in the GL Glargine (91.2%) and the Lantus® groups (90.5%) (Figure 2). The incidences of important protocol deviations (IPDs) were generally similar between treatment groups overall (Table S3), and none of the participants discontinued the study because of IPDs. The final dropout rate was 9.2% at the end of enrolment, and the participant withdrawals (4.1%) were not specifically linked to any of the two IPs.

Demographic characteristics, including age, sex, ethnicity, and body mass index, were well-matched between the groups, as indicated in Table 1. The mean age of participants was 60.8 years, and the mean weight of participants was 98.1 kg. The proportion of men was higher than that of women in the study (60.1% vs. 39.9%, respectively). The population was predominantly white (79.7%). The majority of the participants were not Hispanic or Latino (76.9%). The mean baseline level of HbA1c was comparable between the treatment groups. There were 217 participants (77.2%) with no missing data in the GL glargine and 221 participants (78.4%) in the Lantus®. In addition, 15 participants had 17 events of using non-study defined basal or bolus insulins, mostly because of hospital-prescribed insulin treatment during the participant's hospitalization.

3.2 | Immunogenicity

The proportions of participants testing positive for treatment-induced AIA by week 26 were similar between the GL Glargine (19.2%) and Lantus® (21.3%) treatment groups (Figure 3A). The 90% CI for the

TABLE 1 Demographics and baseline characteristics.

	GL Glargine (N = 284), n (%)	Lantus® (N = 283), n (%)	Total (N = 567), n (%)
Sex, n (%)			
Female	104 (36.6)	122 (43.1)	226 (39.9)
Male	180 (63.4)	161 (56.9)	341 (60.1)
Race, n (%)			
White	227 (79.9)	225 (79.5)	452 (79.7)
Black or African American	35 (12.3)	36 (12.7)	71 (12.5)
Asian	15 (5.3)	12 (4.2)	27 (4.8)
American Indian or Alaska Native	2 (0.7)	1 (0.4)	3 (0.5)
Native Hawaiian or other Pacific Islander	2 (0.7)	1 (0.4)	3 (0.5)
Other	1 (0.4)	5 (1.8)	6 (1.1)
Multiple	2 (0.7)	3 (1.1)	5 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	59 (20.8)	69 (24.4)	128 (22.6)
Not Hispanic or Latino	223 (78.5)	213 (75.3)	436 (76.9)
Not reported	2 (0.7)	1 (0.4)	3 (0.5)
Previous exposure to insulin or analogues, n (%)			
No previous exposure	80 (28.2)	80 (28.3)	160 (28.2)
Previous exposure	204 (71.8)	203 (71.7)	407 (71.8)
Age, years	61.3 (8.98)	60.3 (8.95)	60.8 (8.97)
Weight, kg	98.0 (20.1)	98.1 (20.5)	98.1 (20.3)
BMI, kg/m^2	33.49 (5.6)	33.59 (6.0)	33.54 (5.8)
Duration of diabetes, years	15.2 (7.9)	15.3 (7.9)	15.3 (7.9)
HbA1c, %	8.49 (1.027)	8.51 (1.029)	8.50 (1.027)
AIA result, n (%)			
Negative	252 (88.7)	263 (92.9)	515 (90.8)
Positive	5 (1.8)	1 (0.4)	6 (1.1)
Non-reportable	27 (9.5)	19 (6.7)	46 (8.1)
NAb results, n (%)			
Negative	5 (1.8)	1 (0.4)	6 (1.1)
Positive	0	0	0
Not tested	279 (98.2)	282 (99.6)	561 (98.9)
Oral antidiabetes medications, ≥10% of patients in each treatment group; n (%)			
Metformin	218 (76.8)	221 (78.1)	439 (77.4)
Glipizide	54 (19.0)	63 (22.3)	117 (20.6)
Glimepiride	60 (21.1)	49 (17.3)	109 (19.2)

Note: Data were presented as mean (SD) or n (%).
Abbreviations: AIA, anti-insulin antibody; BMI, body mass index; CRF, case report form; GL Glargine, Gan & Lee Insulin Glargine Injection; HbA1c, glycated haemoglobin treatment group in category; Lantus®, European Union-approved Lantus; N, number of participants in a treatment group; NAb, neutralizing antibody.

difference in proportions (−2.1 percentage points) ranged from −7.6% to 3.5%, falling entirely within the predefined similarity margins (−10.7% to 10.7%). In addition, sensitivity analyses were performed on participants who had no missing data and had completed treatment, and the results were similar to those of the primary analysis (treatment difference −2.7%, 90% CI: −5.6, 0.3) (Table S4). Subgroup analyses assessed the influence of multiple parameters on treatment-induced AIA incidence from baseline to week 26. Notably, similar percentages of participants developed treatment-induced AIA in each subgroup, including those with previous insulin glargine exposure (9.5% for GL glargine and 7.7% for Lantus®) and those without previous insulin glargine exposure (20% for GL glargine and 21.9% for Lantus®) (Table S5). These findings indicate equivalence between the treatment groups in terms of AIA response (Table 2).

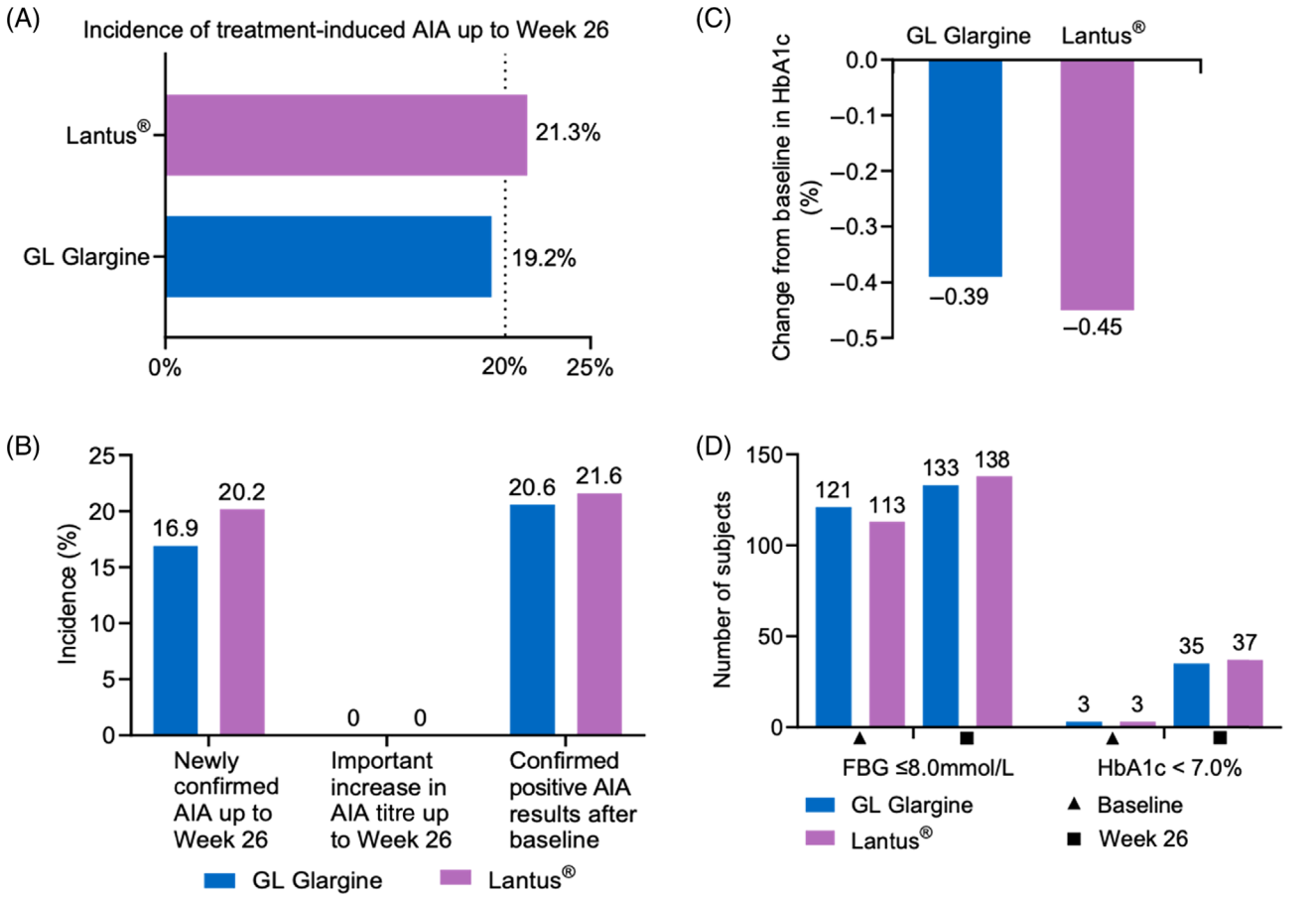

FIGURE 3 Immunogenicity outcomes and efficacy outcomes. (A) Incidence of treatment-induced AIAs up to week 26. (B) Secondary endpoints of immunogenicity. (C) Change from baseline in HbA1c at week 26. (D) Other secondary endpoints of efficacy. Confirmed positive AIA, defined as a participant, is deemed to have confirmed positive AIA at any time point. AIA, anti-insulin antibodies; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; Lantus®, European Union-approved Lantus.

Secondary immunogenicity endpoints were assessed based on the participants' AIA status at baseline. The majority of participants had a negative AIA status at baseline [249 of 281 in the GL Glargine group (88.6%) and 262 of 282 in the Lantus® group (92.9%)]. Similar percentages of these participants exhibited newly confirmed AIA responses at week 26 (16.9% for GL Glargine and 20.2% for Lantus®) (Figure 3B). Among the few participants who tested positive for AIA at baseline (five participants in the GL Glargine group and one in the Lantus® group), none experienced an important increase (≥4-fold increase) in AIA titers during the study. Of the participants who had confirmed positive AIA results after baseline, one participant (10.0%) in the GL Glargine and three (18.8%) in the Lantus® had developed anti-insulin NAbs.

3.3 | Efficacy

At week 26, the analysis revealed a least squares mean difference of 0.06% in the change from baseline in HbA1c between the GL Glargine (−0.39%) and Lantus® treatment groups (−0.45%) (Figure 3C). Equivalence between GL Glargine and Lantus® was evaluated based on the 90% CI of the treatment difference (−0.13%, 0.24%), which was within the predefined equivalence limits (−0.4%, 0.4%). Furthermore, the non-inferiority of GL Glargine compared with Lantus® was evaluated using the 95% CI of the treatment difference (−0.16%, 0.27%), which also fell within the predefined limits for both the first (<0.4%) and second (<0.3%) tests in the hierarchical analysis (Table 3).

The percentages of participants achieving FBG levels of ≤8.0 mmol/L at week 26 were similar between the GL Glargine and Lantus® treatment groups (46.8% and 48.8%, respectively) (Figure 3D). In addition, comparable results were observed between treatment groups in terms of the percentages of participants achieving HbA1c levels <7.0% at week 26 (12.3% for GL Glargine and 13.1% for Lantus®) (Figure 3D). These findings support the noninferiority of GL Glargine compared with Lantus® in terms of efficacy.

In this study, drug exposure was evaluated based on the duration of therapy and the overall average daily dose. The median therapy duration was consistent at 26 weeks for both GL Glargine (ranging from 0.1 to 31.0 weeks) and Lantus® (from 2.0 to

TABLE 2 Immunogenicity outcomes (safety analysis set)

Parameter	GL Glargine (N = 281)	Lantus® (N = 282)
Primary endpoint		
Incidence of treatment-induced AIA up to week 26, n (%)	54 (19.2)	60 (21.3)
Treatment difference (%) 90% confidence interval (%)	−2.1 (3.39) (−7.6, 3.5)	
Secondary endpoints		
Subjects with AIA-negative at baseline	249	262
Incidence of newly confirmed treatment-induced AIA up to week 26, n (%)	42 (16.9) (N = 249)	53 (20.2) (N = 262)
Confirmed AIA-positive at baseline	5	1
Incidence of important increase in AIA titer up to week 26, n (%)	0	0
Incidence of NAbs after baseline up to week 26, n (%)	1 (10.0) (N = 10)	3 (18.8) (N = 16)

Abbreviations: AIA, anti-insulin antibody; GL Glargine, Gan & Lee Insulin Glargine Injection; Lantus®, European Union-approved Lantus; N, number of participants in a treatment group; NAb, neutralizing antibody.

TABLE 3 Efficacy outcomes (full analysis set)

Parameter	GL Glargine (N = 284)	Lantus® (N = 283)
Key secondary endpoint		
Change from baseline in HbA1c at week 26, %, LSM (SE)	−0.39 (0.079)	−0.45 (0.079)
Treatment difference, % (SE)	0.06 (0.111)	
90% CI, %	(−0.13, 0.24)	
95% CI, %	(−0.16, 0.27)	
Other secondary endpoints		
FBG ≤8.0 mmol/L at week 26, n (%)	133 (46.8)	138 (48.8)
HbA1c ≤7.0% at week 26, n (%)	35 (12.3)	37 (13.1)

Abbreviations: CI, confidence interval; FBG, fasting blood glucose; GL Glargine, Gan & Lee insulin glargine injection; HbA1c, glycated haemoglobin; Lantus®, European Union-approved Lantus; LSM, least squares mean; N, number of participants in a treatment group; SE, standard error.

29.6 weeks). Furthermore, the overall participant average daily dose exhibited similarity between the GL Glargine (45.0 ± 28.67 U) and the Lantus® (45.3 ± 32.20 U). A doubling of the daily dose was reported in 33 participants (11.7%) and 41 participants (14.5%) in the GL Glargine and Lantus® after randomization, respectively, compared with the first average daily dose (Table S6). These data suggest that the exposure levels of insulin glargine were equivalent across the respective groups.

TABLE 4 Overview of adverse events (safety analysis set)

Adverse event category	GL Glargine (N = 281), n (%) m	Lantus® (N = 282), n (%) m
Any TEAE	225 (80.1) 1716	230 (81.6) 1598
Any CTCAE grade ≥3 TEAE	18 (6.4) 25	13 (4.6) 15
Any hypoglycaemic TEAE	150 (53.4) 1259	146 (51.8) 1109
Any CTCAE grade ≥3 Hypoglycaemic TEAE	2 (0.7) 2	0
Any IP-related AE	125 (44.5) 854	122 (43.3) 774
Any CTCAE grade ≥3 IP-related TEAE	0	0
Any death	0	0
Any SAE	15 (5.3) 21	16 (5.7) 18
Any IP-related SAE	0	0
Any hypoglycaemic SAE	0	0
Any AE leading to discontinuation of IP	1 (0.4) 2	0
Any IP-related AE leading to discontinuation of IP	0	0

Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; GL Glargine, Gan & Lee insulin glargine injection; IP, investigational product; m, number of events; Lantus®, European Union-approved Lantus; n, number of participants in a treatment group in a category; N, number of participants in a treatment group; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

3.4 | Safety

The frequency and nature of TEAEs reported during the study were consistent with expectations based on the treatments administered. Throughout the 26-week treatment duration, the overall percentage of participants experiencing any TEAE was similar in both the GL Glargine (80.1%) and Lantus® (81.6%) treatment groups. The proportion of participants experiencing serious AEs (SAEs) was low and similar between the GL Glargine (5.3% of participants) and the Lantus® (5.7% of participants) (Table 4). Hypoglycaemia was the most commonly reported TEAE, occurring in approximately half of the participants in each treatment group (Tables S7 and S8). Only a few participants reported any injection site reactions [two participants (0.8%) in the GL Glargine and one (0.4%) in the Lantus®]. There were no clinically relevant differences or changes observed in laboratory, vital signs, electrocardiogram, or continuous glucose monitoring results (Tables S9 and S10) between groups.

The rate of hypoglycaemia events, measured by the rate ratio of the annual rates for the GL Glargine arm versus the Lantus® treatment

arm, did not show a statistically significant difference between the GL Glargine treatment group (2.05 events per year) and the Lantus® treatment group (1.66 events per year) based on the rate ratio of 1.24 (95% CI: 0.90, 1.70; $p = .182$).

4 | DISCUSSION

Both the GL Glargine and Lantus® cohorts showed comparable demographic distributions, encompassing age, gender, race and body mass index. Consistent immunogenicity and efficacy results were observed across diverse demographics in subgroup analyses for both therapeutic arms (Tables S5 and S11).

The FDA and EMA mandate comprehensive assessments of biosimilars, including purity, pharmacokinetics, clinical efficacy, and immunogenicity, to ensure equivalence to reference products, although evolving guidelines may reduce the need for extensive immunogenicity data in future approvals.[27,31,32] Nevertheless, the assessment of insulin's immunogenicity potential continues to be crucial in understanding therapeutic strategies in diabetes management.[17]

Immunogenic reactions to biologics are safety concerns, potentially causing therapeutic neutralization and hypersensitivity reactions.[33] This study shows the immunogenicity bioequivalence of GL Glargine to Lantus® in patients with T2DM, despite variations in treatment-induced AIA incidences influenced by early study withdrawal and data imputation. Notably, consistent results on the incidence of treatment-induced AIA were observed across demographics and previous insulin exposure between treatment groups. In summary, GL Glargine is immunogenically bioequivalent to Lantus®, consistent with previous research.[26,34]

Consistent with previous studies of potential insulin glargine biosimilars, this study was designed to evaluate immunogenicity in people with T2DM.[35] The proportion of treatment-induced AIA in patients with T2DM in this study was similar to that reported in other studies (approximately 20%) but lower than in patients with T1DM (approximately 60%).[36] This discrepancy may be because of the differences in the immune response in patients with T1DM and T2DM, which may affect their respective immunogenicity profiles.[36] In addition, the majority of patients with T1DM were already treated with exogenous insulin therapy before entering clinical trials. Therefore, as expected, the baseline presence of detectable anti-insulin antibodies was higher in patients with T1DM than in insulin-naïve patients with T2DM. In this study, there was a difference in immunogenicity between patients with previous exposure and those with no previous exposure to insulin glargine. However, a previous study showed similar immunogenicity profiles in insulin-naive and insulin-non-naive patients.[37] This discrepancy may be because of the small sample size (21 participants in GL Glargine and 13 in Lantus®) of patients with previous exposure to insulin glargine in our study. Caution should be exercised when comparing anti-drug antibody incidence across studies, as the observed immunogenicity of a compound depends on many factors, including laboratory factors, trial design, and patient population.[38]

The bioequivalence and non-inferiority of GL Glargine to Lantus®, in the context of efficacy, were corroborated by the HbA1c measurements taken at week 26, with the 90% CI for the treatment difference between −0.13 and 0.24. Both the GL Glargine and Lantus® cohorts showed comparable proportions of participants achieving an FBG ≤8.0 mmol/L at baseline and week 26. Hence, GL Glargine shows therapeutic equivalence and noninferiority to Lantus®. These findings are consistent with a phase 1 clamp trial showing bioequivalence between the two insulin types in PK/PD parameters[26] and a study using a continuous glucose monitoring system, indicating that GL Glargine exhibited clinical non-inferiority to Lantus® in the management of T2DM.[39]

Safety is paramount for insulin products, with primary concerns including hypoglycaemia, allergic reactions, and so on.[40] The incidence of TEAEs, including their severity and relationship to IP, was similar between the GL Glargine and Lantus® treatment groups. Hypoglycaemia, a significant concern in diabetes management,[41] was experienced by roughly half of the participants in both groups and was predominantly mild to moderate in severity, consistent with previous studies showing a hypoglycaemic incidence of approximately 48% in patients with T2DM using biosimilar glargine.[36] This observation aligns with real-world data from the introduction of insulin glargine. Notably, hypoglycaemia stands out as the most prevalent AE for marketed Gan & Lee glargine, accounting for nearly 40% of the total AEs since the launch of GL glargine. The most frequent SAEs were chest pain, non-cardiac chest pain, osteomyelitis, skin ulcer and syncope, all reported in two participants and none considered IP-related. Only one participant in the GL Glargine discontinued because of TEAEs of pancreatic mass and pancreatic carcinoma, which were also not considered IP-related.

One potential limitation of this investigation was its open-label design. To mitigate the risk of operational bias influencing the study outcomes and to enhance the interpretability and robustness of the data, certain roles within the sponsor and study team were maintained under blinding, including the immunogenicity consultant and the bioanalytical vendor responsible for immunogenicity assessments. Consequently, the study design is unlikely to have impacted the results.

In conclusion, the study affirms the bioequivalence of GL Glargine and Lantus® in terms of immunogenicity, safety, and efficacy for adult patients with T2DM. Consistent with previous studies showing PK/PD bioequivalence in patients with T1DM, this study further substantiates the bioequivalence of GL Glargine to Lantus®.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis and study conduct, and EAC contributed to the manuscript editing. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of these studies are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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