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Original Article

Immunogenicity, Efficacy, and Safety of Biosimilar Insulin Glargine (Gan & Lee Glargine) Compared With Originator Insulin Glargine (Lantus) in Patients With Type 1 Diabetes After 26 Weeks Treatment

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ABSTRACT

Objective: To compare the immunogenicity, safety, and efficacy of Gan & Lee insulin glargine (GL Glargine) with that of the originator insulin glargine (Lantus) in patients with type 1 diabetes mellitus (T1DM).

Methods: This was a phase 3, multicenter, randomized, open-label, equivalence study. Five hundred seventy-six subjects with T1DM were randomized 1:1 to receive either GL Glargine or Lantus treatment for 26 weeks. The primary end point was the percentage of subjects in each treatment group who developed treatment-induced anti-insulin antibody after baseline and up to visit week 26, which was evaluated using a country-adjusted logistic regression model. The study also compared the changes in glycated hemoglobin, and adverse events including hypoglycemia.

Abbreviations: AE, adverse event; AIA, anti-insulin antibody; CI, confidence interval; DM, diabetes mellitus; EMA, European Medicines Agency; EU, European Union; FBG, fasting blood glucose; FDA, Food and Drug Administration; GL Glargine, Gan & Lee insulin glargine; HbA1c, glycated hemoglobin; IP, investigational product; Lantus, originator insulin glargine; NAb, neutralizing antibody; PD, pharmacodynamic; PK, pharmacokinetic; SAE, serious adverse event; T1DM, type 1 diabetes mellitus; TEAE, treatment-emergent adverse event.

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immunogenicity
insulin glargine
biosimilar
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Results: The percentage of subjects positive for treatment-induced anti-insulin antibody by Week 26 was 25.8% in the GL Glargine treatment group and 25.3% in the Lantus treatment group, with a 90% confidence interval (−5.4, 6.5) of the difference in proportions that fell completely between the similarity margins (−11.3, 11.3). The least squares mean difference between treatment groups for changes in glycated hemoglobin was −0.08 (90% confidence interval: −0.23, 0.06), and the other immunogenicity and safety profiles were comparable.

Conclusion: GL Glargine demonstrated similar immunogenicity, efficacy, and safety compared to Lantus over 26 weeks in patients with T1DM.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose levels resulting from absolute or relative insulin deficiency in the context of β-cell dysfunction, insulin resistance, or both.[1] DM comprises various subtypes, among which type 1 diabetes mellitus (T1DM) is one condition characterized by the autoimmune destruction of pancreatic β-cells, leading to little or no production of insulin.[2-4] Thus, individuals with T1DM depend on the supplement of exogenous insulin to manage blood glucose levels and to prevent or slow diabetes complications.[4-6] An optimal insulin replacement therapy aims to emulate physiological blood glucose regulation, ensuring a balance that accommodates variations in dietary intake and physical activity.[7] For T1DM, standard insulin replacement regimens consist of basal insulin plus several injections of mealtime insulin or continuous insulin infusion by subcutaneous pump.[7,8]

Basal insulin includes the premixed neutral protamine Hagedorn insulin and the long-acting insulin analogs,[7] shows that insulin analogs have a longer duration of action with more stable plasma levels than neutral protamine Hagedorn. Nevertheless, the cost of these analogs has significantly increased over the last 20 years, far exceeding the rise in other medical expenses. This cost surge is exacerbating financial burdens for patients with diabetes and is associated with reduced medication adherence.[9] Furthermore, the accessibility and affordability of insulin analogs are significantly lower in low-to-middle-income countries compared to high-income ones, where these issues also persist.[10,11] To reduce the rising burden of insulin therapy worldwide, biosimilar insulins have been developed in recent years. A biosimilar is a biological product that is highly similar to another already approved product with no clinically meaningful differences in terms of safety, quality, or potency/efficacy.[12,13] Prescribing biosimilar insulins would decrease medication costs without losing safety and efficacy, increase accessibility to insulin therapy, and expand cost-effective insulin options for patients.[14,15] To date, several biosimilar insulin analogs are available globally, including 9 in the United States/European Union (EU) and 19 in China, with 3 long-acting types like Basaglar, Semglee, and Rezvoglar in the United States/EU and more in development.[16]

Currently, there are 4 commonly prescribed long-acting basal insulin analogs: insulin glargine (U100), insulin detemir, insulin degludec, and insulin glargine U300. Of these 4 basal insulins, insulin glargine is the predominant one. Insulin glargine (originator insulin glargine [Lantus], Sanofi-Aventis) was the first long-acting insulin analog to receive approval from the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in 2000, allowing for once-daily basal insulin injection in patients with DM.[17] Until now, insulin glargine has been the leading product in the basal insulin markets, constituting approximately 50% of the global basal insulin market share.[18] Basalin, a biosimilar introduced in China in 2005 by Gan & Lee Pharmaceuticals, has been approved in 19 countries and has consistently shown sales growth. This is in line with efforts to reduce global basal insulin analog costs.

Basalin (referred to as Gan & Lee insulin glargine [GL Glargine]) has a primary amino acid sequence identical to originator insulin glargine (Lantus) and has been demonstrated to have comparable pharmacokinetic (PK) and pharmacodynamic (PD) between GL Glargine and the Lantus in patients with T1DM per the FDA and the EMA's regulations on biosimilar insulins.[19-22] Based on this, 2 phase 3 immunogenicity studies of this proposed biosimilar insulin were conducted according to the requirements of the US and EU regulations.[19,23] These are the results of the phase 3 study that was conducted in patients with T1DM to compare the immunogenicity, safety, and efficacy of GL Glargine with that of Lantus.

Methods

Study Design

This was a multicenter, randomized, open-label, phase 3 study conducted at 83 sites in 6 countries comparing the immunogenicity, safety, and efficacy of GL Glargine with Lantus in subjects with T1DM. There was a screening period of up to 2 weeks followed by a 26-week randomization visit and a 30-day follow-up visit. During the screening period, subjects had their basal insulin dosing optimized (Supplementary Table 1). The dosage of investigational product (IP) was determined by the physician, according to the requirement of the subject. Subjects who met the eligibility criteria were randomized 1:1 in an open-label fashion to receive either GL Glargine or Lantus using an Interactive Web Response System (Supplementary Fig. 1). Participants were stratified by country. The key inclusion/exclusion criteria are listed in the Supplementary Material. The study was conducted in full accordance with the International Council for Harmonisation for Good Clinical Practice and Declaration of Helsinki and approved by the Institutional Review Board according to national or local regulations. Written informed consent was obtained from all participants.

Study End Points and Assessments

The primary end point was the percentage of subjects in each treatment group who developed treatment-induced anti-insulin antibody (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. The secondary immunogenicity end point included the percentage of subjects with anti-insulin neutralizing antibodies (NAbs) from baseline up to week 26. The immunogenicity assessment used the one-assay[24] and tiered approach.[25] Samples collected before dosing (baseline, week 12, and week 26) in both treatment groups were first validated using the electro-chemiluminescence bridging assay to detect and confirm the presence of binding AIA in human serum using a screening and confirmatory assay. Samples that tested positive in the confirmatory assay, the antibody titer and the presence of NAbs were determined.

The key secondary end point was the change in glycated hemoglobin (HbA1c) from baseline at visit week 26. Other secondary efficacy end points included the percentage of subjects with fasting blood glucose (FBG) levels of ≤6.0 mmol/L and HbA1c <7.0% at week 26. Safety evaluations included: the incidence and severity of all treatment-emergent adverse events (TEAEs), the incidence of clinically significant laboratory abnormalities, and the incidence of clinically significant abnormalities in electrocardiogram and vital signs. Additionally, the continuous glucose monitoring data were collected for the rate of hypoglycemia.

Statistical Analysis

An overview of subject disposition and analysis sets is shown in Fig. 1. Safety and immunogenicity analyses were based on the safety analysis set which consisted of all randomized subjects who received any IP according to actual treatment received. Efficacy analyses were performed using the full analysis set which consisted of all randomized subjects and were based on randomized treatment.

The primary analysis for the primary immunogenicity end point was an equivalence test comparing the limits of the 90% confidence interval (CI) for treatment-induced AIA development to the prespecified margins (−margin, +margin); the margins were dependent on the unadjusted treatment-induced AIA rate in the Lantus treatment group. Equivalence was considered to be demonstrated if the entire 90% CI fell within the predefined similarity margins (−11.3, 11.3). The number and percentage of subjects in each treatment group who developed treatment-induced AIA up to visit week 26 was evaluated using a country-adjusted logistic regression model. Missing outcomes were imputed following an intent-to-treat approach. Sensitivity analyses were performed using alternative analysis sets and assumptions to evaluate the impact of important protocol deviations (overall and immunogenic-interfering) and premature discontinuations from treatment and/or the study.

The key secondary end point analysis was to evaluate equivalence (FDA)/noninferiority (EMA) of GL Glargine relative to Lantus for HbA1c, by comparing the 90% CI with (−0.4%, 0.4%) for equivalence using the 2 one-sided tests and by comparing the upper limit of the 95% CI with 0.4% for noninferiority from a pattern mixture model that uses multiple imputations analyzed using analysis of covariance with treatment and stratification factor of the country included as a fixed effect and baseline HbA1c included as a covariate. For the noninferiority evaluation, analysis of HbA1c followed a hierarchical testing strategy: first, noninferiority was tested with a

Highlights

- The study compared immunogenicity of GL Glargine and Lantus in patients with T1DM.
- This was a phase 3, randomized, open-label, multicenter, equivalence study.
- GL Glargine exhibited similar immunogenicity, efficacy, and safety with Lantus.
- This study may provide a cost-effective insulin option for patients with diabetes.

Clinical Relevance

Biosimilar insulins have been developed to address the increasing financial burden of originator insulins and improve the accessibility and affordability. GL Glargine has demonstrated comparable pharmacokinetics and pharmodynamics to the originator insulin glargine (Lantus) in patients with T1DM. In this phase 3 study, GL Glargine exhibited comparable immunogenicity, efficacy and safety profiles with Lantus in patients with T1DM. This further substantiates the clinical evidence supporting the equivalence of GL Glargine to Lantus and may provide a cost-effective insulin option for patients with diabetes.

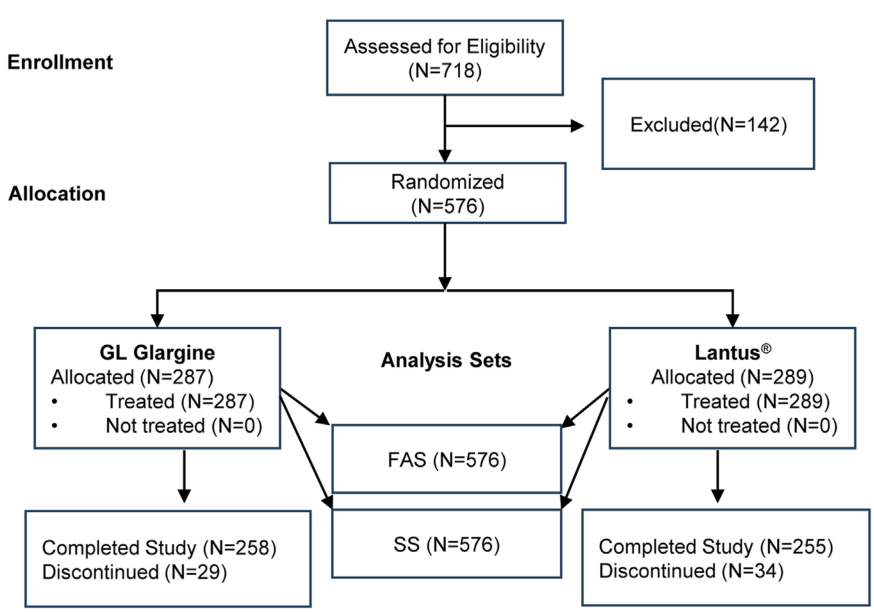

Fig. 1. Disposition and analysis sets. *FAS* = full analysis set; *GL Glargine* = Gan & Lee insulin glargine; *Lantus* = originator insulin glargine; *N* = number of subjects; *SS* = safety analysis set.

margin of 0.4%; secondly, if the test using a margin of 0.4% was significant, then noninferiority was tested using a margin of 0.3%. The other secondary immunogenicity and efficacy variables were analyzed based on a logistic regression model similar to that used in the primary analysis of the primary immunogenicity end point. Hypoglycemia event rate was compared between treatment groups using a negative binomial regression model. The response variable in the model was the number of hypoglycemia events, and the model included factors for the treatment group and site.

Results

Demographics and Baseline Characteristics

In the study, 718 subjects were screened and 576 were randomly assigned (GL Glargine, *N* = 287; Lantus, *N* = 289). The most frequent reasons for screen failures (≥10% of subjects) were exclusion criteria met (28.9%), inclusion criteria not met (16.9%), and withdrew consent (14.1%). A total of 513 subjects (89.1%) completed the study, with similar percentages of subjects in the GL Glargine treatment group (89.9%) and the Lantus treatment group (88.2%). Demographics and baseline characteristics, including age, sex, race, ethnicity, weight, body mass index and HbA1c were similar between treatment groups (Table 1).

Immunogenicity

The percentage of subjects positive for treatment-induced AIA (composite of a newly developed or important increase in AIA) by week 26 was similar between the GL Glargine treatment group (25.8%) and Lantus treatment group (25.3%), with a 90% CI (−5.4, 6.5) of the difference in proportions (0.6 percentage points; asymptotic standard error: 3.63) that fell completely between the similarity margins (−11.3, 11.3) for equivalence (Table 2; Fig. 2, *A* and *B*). In addition, sensitivity analyses without imputation were performed and the results were similar to those of the primary analysis (90% CI: −4.3, 4.6).

Regarding secondary immunogenicity variables, most subjects had a negative AIA status at baseline (236 [GL Glargine] versus 239 [Lantus]), and similar percentages of these subjects had newly confirmed AIA responses at week 26 (26.7% versus 24.7%). Of the subjects who were positive for AIA at baseline, the incidence of subjects who had an important increase (≥4-fold increase) in AIA titer during the study was modestly higher in the Lantus treatment group (29.2%) than in the GL Glargine treatment group (22.4%), with a 90% CI (−21.1, 8.9) of the difference in proportions (−6.1 percentage points; asymptotic standard error: 9.12). Subjects with confirmed positive AIA results after baseline were evaluated for anti-insulin NAbs. The percentage of subjects who developed anti-insulin NAbs was similar between treatment groups by week 26 (24.1% versus 26.7%) (Table 2).

Efficacy

At week 26, the least squares mean difference between treatment groups in change from baseline in HbA1c was −0.08%. Equivalence between the GL Glargine and Lantus was evaluated, based on the 90% CI of the treatment difference (−0.23%, 0.06%), which was within the predefined equivalence limits (−0.4%, 0.4%) (Fig. 2 *C* and *D*). Noninferiority of GL Glargine compared to Lantus was also evaluated, based on the 95% CI (−0.26%, 0.09%) of the treatment difference, which was within the predefined limit for the first test (<0.4%) and the second test in the hierarchy (<0.3%) (Table 3).

Table 1
Demographics and Baseline Characteristics (Full Analysis Set)

Characteristics	GL Glargine (*N* = 287)	Lantus (*N* = 289)	Total (*N* = 576)
Sex			
Female	103 (35.9)	112 (38.8)	215 (37.3)
Male	184 (64.1)	177 (61.2)	361 (62.7)
Age, y	45.70 ± 13.96	46.70 ± 14.46	46.20 ± 14.21
Race			
White	262 (91.3)	265 (91.7)	527 (91.5)
Black or African American	13 (4.5)	14 (4.8)	27 (4.7)
Asian	6 (2.1)	7 (2.4)	13 (2.3)
American Indian or Alaska Native	0	1 (0.3)	1 (0.2)
Native Hawaiian or other Pacific Islander	2 (0.7)	0	2 (0.3)
Other	2 (0.7)	1 (0.3)	3 (0.5)
Multiple	2 (0.7)	1 (0.3)	3 (0.5)
Ethnicity			
Hispanic or Latino	23 (8.0)	16 (5.5)	39 (6.8)
Not Hispanic or Latino	259 (90.2)	272 (94.1)	531 (92.2)
Not reported	4 (1.4)	1 (0.3)	5 (0.9)
Unknown	1 (0.3)	0	1 (0.2)
Weight, kg	80.90 ± 13.43	81.55 ± 16.40	81.23 ± 14.98
BMI, kg/m^2	27.01 ± 3.88	27.11 ± 4.24	27.06 ± 4.06
Country			
Czech Republic	24 (8.4)	25 (8.7)	49 (8.5)
Germany	29 (10.1)	28 (9.7)	57 (9.9)
Hungary	20 (7.0)	21 (7.3)	41 (7.1)
Poland	37 (12.9)	37 (12.8)	74 (12.8)
Spain	26 (9.1)	28 (9.7)	54 (9.4)
United States of America	151 (52.6)	150 (51.9)	301 (52.3)
Duration of diabetes, y	20.20 ± 13.88	21.70 ± 13.95	21.00 ± 13.92
Previous exposure to insulin glargine	200 (69.7)	208 (72.0)	408 (70.8)
HbA1c, %	8.11 ± 1.23	8.08 ± 1.27	8.10 ± 1.25

Data were presented as mean ± SD or n (%).
Abbreviations: BMI = body mass index; GL Glargine = Gan & Lee insulin glargine; HbA1c = glycosylated hemoglobin; Lantus = originator insulin glargine; n = number of subjects in a treatment group in a category; N = number of subjects in a treatment group; SD = standard deviation.

Table 2
Immunogenicity Outcomes (Safety Analysis Set)

Parameter	GL Glargine (*N* = 287)	Lantus (*N* = 289)
Primary end point		
Incidence of treatment-induced AIA up to week 26, n (%)	74 (25.8)	73 (25.3)
Treatment difference, %, (ASE) 90% CI, %	0.6 (3.63) (−5.4, 6.5)	
Other Secondary end points		
Subjects with negative AIA at baseline	236	239
Incidence of newly confirmed AIA up to week 26, n (%)	63 (26.7)	59 (24.7)
Subjects with AIA positive at baseline	49	48
Incidence of important Increase in AIA titer up to Week 26, n (%)	11 (22.4)	14 (29.2)
Subjects with confirmed AIA after baseline without data imputation	54	60
Incidence of NAbs up to week 26, n (%)	13 (24.1)	16 (26.7)

Note: Treatment differences and associated CI are presented for GL Glargine treatment group minus the Lantus treatment group.
Abbreviations: AIA = anti-insulin antibody; ASE = asymptotic standard error; CI = confidence interval; GL Glargine = Gan & Lee insulin glargine; Lantus = originator insulin glargine; n = number of subjects in a treatment group in a category; N = number of subjects in a treatment group; NAbs = anti-insulin neutralizing antibodies.

Other secondary efficacy end points evaluated measures of glycemic control, proportions of subjects with FBG levels of ≤6.0 mmol/L and HbA1c <7.0% at week 26. Results were similar between treatment groups for both parameters (Table 3).

Study drug exposure was assessed using the duration of therapy and overall subject average daily dose. The median duration of therapy was identical between groups: 26 weeks (1.4-37.4 weeks) and 26 weeks (1.9-31 weeks) in the GL Glargine and Lantus treatment groups, respectively. The overall subject average daily dose was similar between the GL Glargine treatment group (29.56 ± 16.05 U) and the Lantus treatment group (28.96 ± 17.59 U) with no significant difference between groups (P = .670). These results suggest that the exposure of insulin glargine was comparable between groups.

Safety

During the 26-week treatment period, the overall percentage of subjects with any TEAEs was similar between the GL Glargine (90.2%) and Lantus (92.4%) treatment groups. There was one death during the study. The fatal event was a serious adverse event of sepsis, which occurred in a subject in the Lantus treatment group and was assessed as not related to IP. The proportion of subjects with serious adverse events was low and similar between treatment groups (3.5% versus 4.8%). In each treatment group, 2 subjects discontinued the study due to adverse events (AEs), all of which were assessed as not related to IP. No injection site reactions were reported (Table 4). There were no clinically relevant differences or changes observed in laboratory, electrocardiogram, vital

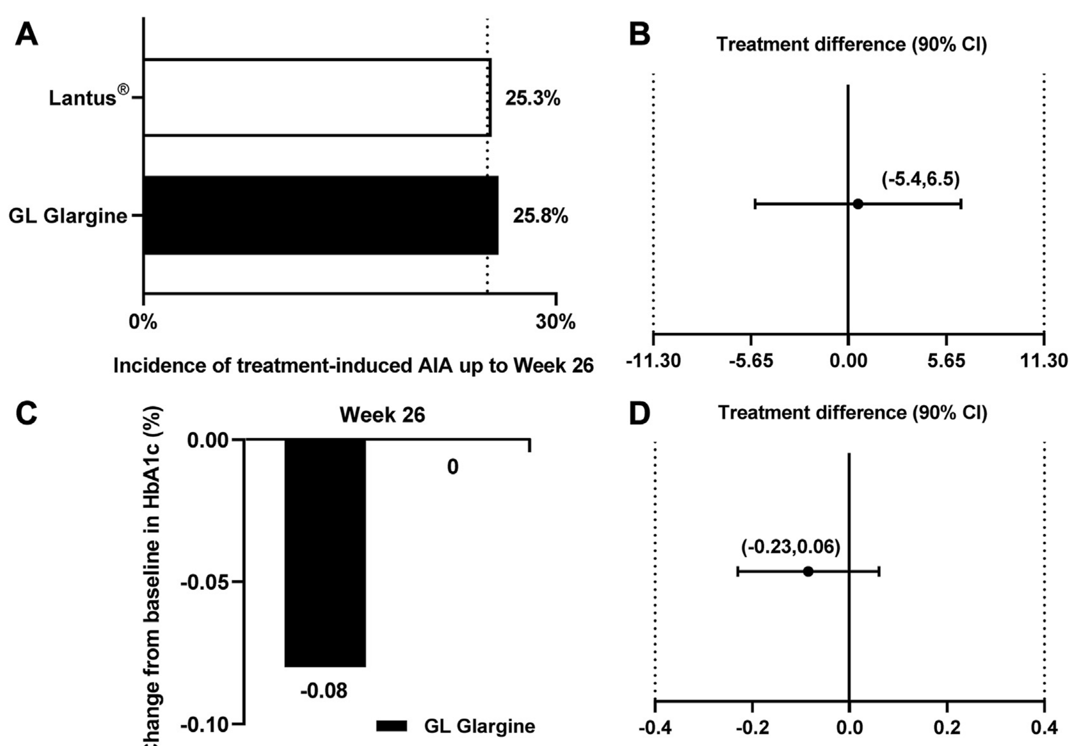

Fig. 2. The incidence of treatment-induced AIA up to week 26 (*A*), and the treatment difference in proportions between the GL Glargine treatment group and Lantus treatment group showing the 90% CI for equivalence (*B*). The least squares mean change in HbA1c (%) from baseline at week 26 (*C*), and the treatment difference in HbA1c (%) between the GL Glargine treatment group and Lantus treatment group showing the 90% CI for equivalence (*D*). *AIA* = anti-insulin antibody; *CI* = confidence interval; *GL Glargine* = Gan & Lee insulin glargine; *HbA1c* = glycosylated hemoglobin; *Lantus* = originator insulin glargine.

Table 3
Efficacy Outcomes (Full Analysis Set)

Parameter	GL Glargine ($N = 287$)	Lantus ($N = 289$)
Key secondary end point		
Change from baseline in HbA1c at week 26, %, LS mean (SE)	−0.08 (0.07)	0.00 (0.06)
Treatment difference, %, (SE)	−0.08 (0.09)	
90% CI, %	(−0.23, 0.06)	
95% CI, %	(−0.26, 0.09)	
Other secondary end points		
FBG ≤6.0 mmol/L at week 26, n (%)	39 (13.6)	42 (14.5)
HbA1c < 7.0% at week 26, n (%)	46 (16.0)	44 (15.2)

Note: Treatment differences and associated CI are presented for GL Glargine treatment group minus the Lantus treatment group.
Abbreviations: CI = confidence interval; FBG = fasting blood glucose; GL Glargine = Gan & Lee insulin glargine; HbA1c = glycosylated hemoglobin; Lantus® = originator insulin glargine; LS = least squares; n = number of subjects in a treatment group in a category; N = number of subjects in a treatment group; SE = standard error.

signs, or continuous glucose monitoring results between treatment groups.

Hypoglycemia was the most frequently reported TEAE, with approximately 85% of subjects in each treatment group experiencing hypoglycemic TEAEs, the majority of which were mild or moderate in severity (Table 4; Supplementary Table 2). The hypoglycemia event rate did not show any statistically significant difference between GL Glargine treatment group (43.97 events per year) versus Lantus treatment group (45.10 events per year) based on the rate ratio (0.97 [95% CI: 0.81, 1.17], $P = .783$) (Supplementary Table 3).

Discussion

This study enrolled a total of 576 with a confirmed diagnosis of T1DM who had been on an approved basal and bolus insulin regimen for at least 6 months, among which 287 participants received GL Glargine and 289 participants received Lantus. Baseline participant characteristics were well balanced in the GL Glargine and Lantus treatment groups, suggesting that baseline characteristics should not influence the outcomes of the study.

Table 4
Safety Outcomes (Safety Analysis Set)

Parameter	GL Glargine ($N = 287$)	Lantus ($N = 289$)
Any TEAE[a]	259 (90.2)	267 (92.4)
Grade 1	129 (44.9)	134 (46.4)
Grade 2	80 (27.9)	81 (28.0)
Grade 3	36 (12.5)	39 (13.5)
Grade 4	14 (4.9)	12 (4.2)
Grade 5	0	1 (0.3)
Any IP-related TEAE	160 (55.7)	161 (55.7)
Any death	0	1 (0.3)
Any SAE	10 (3.5)	14 (4.8)
Any IP-related AE leading to discontinuation	0	0
Injection site reactions	0	0
Any hypoglycemic TEAE	246 (85.7)	254 (87.9)
Any hypoglycemic SAE	3 (1.0)	1 (0.3)

Data were presented as n (%).
Abbreviations: AE = adverse event; CTCAE = common terminology criteria for adverse event; GL Glargine = Gan & Lee insulin glargine; IP = investigational product; Lantus = originator insulin glargine; n = number of subjects in a treatment group in a category; N = number of subjects in a treatment group; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] The severity of TEAEs was presented by CTCAE grade.

The immunogenic response to biologics has long been a safety concern that cannot be ignored in the development of biosimilars. Certain immunoreactions may lead to therapeutic neutralization and hypersensitivity reactions. Therefore, for biosimilar insulins development, there have been regulatory requirements for immunogenicity studies on a case-by-case scenario.[26-29] For this purpose, the present clinical study was conducted to evaluate the immunogenicity of the GL Glargine compared with its Lantus. However, regulations have evolved so that the phase 3 immunogenicity study may be waved for biosimilar insulins recently. Although the present study may not be considered mandatory of regulatory requirement, it maintains its value by providing the direct clinical evidence of the comparable immunogenicity between GL Glargine and the Lantus.[19,23]

Study results showed that GL Glargine and Lantus have similar immunogenicity in the study population (25.8% versus 25.3%), with 90% CI of the difference in the percentage of treatment-induced AIA between treatment groups falling completely within the similarity margins. Furthermore, sensitivity analyses without imputation in the safety analysis set were similar, confirming the robustness of the primary end point result. Overall, these results supported the similar immunogenicity profiles of GL Glargine and Lantus.

In our studies, the proportion of treatment-induced AIA was higher in patients with T1DM (25.5%) than in those with T2DM (20.2%), which is consistent with previous studies.[30] The different immune responses in patients with T1DM and T2DM may influence the immunogenicity profiles.[31] In addition, the proportion of treatment-induced AIA after glargine injection was lower than that reported in other studies, where it was approximately 50%.[30] This discrepancy could be due to differences in the patient populations. It is important to acknowledge that various factors, including patient population, study design, laboratory factors, and analytical approaches, can contribute to variations in immunogenicity profiles across studies.[30,32] Therefore, it is adequate to demonstrate similar immunogenicity profiles in an intrastudy.

Equivalence and noninferiority of GL Glargine compared to Lantus concerning efficacy were demonstrated based on the change of HbA1c level over 26 weeks. This result was further supported by other secondary efficacy end points, including the number and percentage of subjects who achieve a FBG test result of ≤6.0 mmol/L (≤108.0 mg/dL) and who achieve a HbA1c of <7.0% at visit week 26. In general, the euglycemic clamp study, a study to measure insulin action on glucose utilization by interpreting the glucose infusion rate generated, is considered pivotal because glucose infusion rate is much more sensitive than HbA1c in evaluating insulin efficacy.[33] The efficacy results in the present study consistent with the previous phase 1 euglycaemic clamp PK/PD study.[22] Both the phase 1 and phase 3 studies indicated that GL Glargine has equivalent efficacy profiles compared to the originator insulin glargine (Lantus).

Demonstrating a similar safety profile is critical for a proposed biosimilar to acquire marketed approval. Overall, the number and type of TEAEs reported were consistent with treatment expectations. During the 26-week treatment period, the incidences of TEAEs and by categories such as severity and relationship to IP were generally comparable between patients receiving GL Glargine and Lantus. Of these, hypoglycemia was prespecified an AE of special interest. As expected, hypoglycemia was the most frequently reported TEAEs, accounting for 95% of cases and occurring at least once in nearly 85% of subjects in each treatment group. Although a large number of hypoglycemic TEAEs were observed, most were mild or moderate in severity and it did not show any statistically significant difference between the treatment groups. The high incidence of hypoglycemic events could be related to the fact that in addition to the TEAEs reported by the investigators, study patients were instructed to record any hypoglycemic events based on symptoms or actual glucometer measurements. This creates in effect a double-counting of events but ensures that all events are captured. In fact, according to the postmarketing surveillance of GL Glargine, the incidence of AEs is modest and hypoglycemic AEs only accounts for approximately 40% of all AEs compared to the 95% in the present study. In addition, it should be noted that the incidence of hypoglycemia can be affected by many factors, such as the use of bolus insulin and patients' behavior in diabetes control and dose titration.[34]

This study was open-label, which was a possible limitation. However, to avoid the introduction of operational bias into the final study results and to increase the interpretability and reliability of the data, certain study team members were blinded, including the immunogenicity consultant and bioanalysis vendor for immunogenicity analysis. Therefore, the open-label design should not influence the results.

Conclusion

In summary, the results affirmed the equivalence of immunogenicity, safety, and efficacy of GL Glargine and Lantus in patients with T1DM. Combined with previous studies demonstrating PK/PD bioequivalence in patients with T1DM, this study adds to the clinical evidence supporting the equivalence of GL Glargine to Lantus.

Disclosure

The authors have no conflicts of interest to disclose.

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