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ORIGINAL RESEARCH

Efficacy and Safety of LY2963016 Insulin Glargine in Chinese Patients with Type 1 Diabetes Previously Treated with Insulin Glargine (Lantus®): a Post Hoc Analysis of a Randomized, Open-Label, Phase 3 Trial

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ABSTRACT

Introduction: LY2963016 insulin glargine (LY IGlar), a biosimilar of Lantus® insulin glargine (IGlar), demonstrated comparable efficacy and safety versus the reference product in Chinese patients with type 1 diabetes mellitus (T1DM) in the randomized, phase III ABES trial. This post hoc analysis aimed to provide the first evidence for switching from IGlar to LY IGlar in Chinese patients with T1DM.

Methods: This analysis included 210/272 patients with T1DM (77.2%) from the ABES trial who were receiving IGlar at screening. We compared antihyperglycemic efficacy, safety, and immunogenicity in patients randomized to LY IGlar (n = 104) versus those who continued to receive IGlar (n = 106).

Results: There was no significant difference between groups in least-squares mean (LSMean) change in HbA1c from baseline to 24 weeks (LY IGlar − 0.10%, IGlar − 0.08%; LSMean difference [95% confidence interval] − 0.02% [− 0.24, 0.19]). At 24 weeks (last observation carried forward), a similar proportion of patients in each group achieved glycated hemoglobin less than 7.0% (LY IGlar 26.5%, IGlar 32.1%; P = 0.447) and 6.5% or less (LY IGlar 16.7%, IGlar 20.8%; P = 0.482). There were no significant differences between groups in LSMean of self-monitored blood glucose values, or total or basal insulin dose at 24 weeks. Patients in the LY IGlar and IGlar groups had a similar incidence of total hypoglycemia (blood glucose level 70 mg/dL or less, 91.4% vs. 92.5%) and treatment-emergent adverse events (AEs; 75.0% vs. 67.0%), and a low and similar incidence of serious AEs, injection site AEs, and allergic AEs. Similar proportions of patients in the LY IGlar and IGlar groups had treatment-emergent antibody responses (LY IGlar 27.2%, IGlar 28.3%) and detectable insulin antibodies (LY IGlar 52.4%, IGlar 53.8%).

Conclusion: In Chinese patients with T1DM previously treated with IGlar, switching to LY IGlar for 24 weeks resulted in similar efficacy

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and safety outcomes as remaining on IGlar therapy.
Clinical Trial Registration: NCT03338023.

Keywords: Biosimilar; Insulin glargine; Lantus; LY2963016; Switching; Type 1 diabetes

Key Summary Points

Why carry out this study?

LY2963016 insulin glargine (LY IGlar) is an insulin glargine (Lantus®; IGlar) biosimilar that demonstrated comparable efficacy and safety to IGlar in the randomized, 24-week, phase III ABES trial in Chinese patients with type 1 diabetes mellitus (T1DM).

The first biosimilar insulin was launched in China in 2021 and more are expected to become available in the near future; however, there is currently a lack of evidence for switching from originator to biosimilar insulins in this patient population.

To provide the first evidence for switching to LY IGlar from IGlar in Chinese patients with T1DM, we conducted a post hoc subgroup analysis comparing outcomes with LY IGlar and IGlar among patients who were receiving IGlar at screening.

What was learned from the study?

Among patients receiving pre-study IGlar, there were no significant differences between LY IGlar and IGlar in clinical efficacy at 24 weeks (glycated hemoglobin change or target attainment, self-monitored blood glucose levels, insulin dose), safety (hypoglycemia, adverse events), or immunogenicity (treatment-emergent antibody response, insulin antibodies).

This post hoc subgroup analysis of a randomized phase III trial supports switching patients with T1DM to LY IGlar from IGlar in clinical practice.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease in which loss of pancreatic beta cells leads to endogenous insulin deficiency, hyperglycemia, and a lifelong requirement for insulin therapy [1, 2]. More than 500,000 new cases are diagnosed each year and 22 million people are estimated to be living with T1DM worldwide [3]. In China, the incidence of T1DM is lower than in Western countries but has been rising steadily over the past decades [4–6]. According to a recent population-based study, the annual incidence of T1DM per 100,000 in China increased from 2.72 in 2007 to 3.60 in 2017 [6], which is considerably higher than earlier estimates [7]. The economic burden of T1DM is substantial, with costs per patient that exceed those of type 2 diabetes mellitus (T2DM) [8].

The mainstay of therapy for T1DM consists of insulin replacement therapy aiming to achieve tight glycemic control while minimizing hypoglycemia [1]. Insulin therapy is typically implemented through multiple daily insulin injections, and more rarely using continuous subcutaneous insulin infusion. A multi-injection insulin treatment schedule will usually include long-acting basal insulin and fast-acting mealtime (bolus) insulin, to mimic endogenous insulin production [1]. The first approved and most widely used long-acting basal insulin analogue is insulin glargine (IGlar; Lantus®; Sanofi-Aventis, Paris, France [recombinant deoxyribonucleic acid origin]) [9], which provides comparable glycemic control vs. neutral protamine Hagedorn insulin, with fewer hypoglycemic episodes [10, 11].

A biosimilar is a version of an approved biologic medicine (i.e., the originator product) that must demonstrate highly similar physicochemical characteristics, biologic activity, pharmacology, efficacy, and safety compared with the originator to gain regulatory authorization [12]. Recently, biosimilar versions of IGlar have been developed with the potential to reduce direct healthcare costs and improve access to this medication [13]. LY2963016 insulin glargine (LY IGlar) is an IGlar biosimilar

that has an identical primary amino acid sequence, pharmaceutical form, and strength compared with the originator product [14–16]. It was the first approved insulin biosimilar in the European Union and has also been authorized as a follow-on insulin in the USA [17, 18]. The biosimilarity of LY IGlar vs. IGlar was established in a comprehensive clinical development program that included studies in both Chinese and international populations [14, 16, 19–24]. LY IGlar and IGlar demonstrated comparable pharmacokinetic and pharmacodynamic characteristics in healthy volunteers in separate phase I euglycemic clamp trials conducted in China, Singapore, and South Africa [19–21]. In randomized phase III studies in patients with T1DM already receiving basal-bolus regimens, LY IGlar and IGlar showed similar efficacy, safety, and immunogenicity in the ABES trial in Chinese patients [22], and in the global ELEMENT-1 trial in predominantly white patients [14, 25]. Randomized phase III studies have also established the biosimilarity of LY IGlar and IGlar in T2DM, including a trial in Chinese patients (ABET) [23], an international trial in predominantly white patients (ELEMENT-2) [16, 25], and an international trial including a high proportion of Asian patients (ELEMENT-5) [24].

With the availability of biosimilar insulin analogues, switching patients from the originator to a biosimilar product becomes a potential strategy to reduce the cost of diabetes treatment and improve medication access [13, 26]. The practice of switching may be supported by studies demonstrating that patients already receiving the originator product do not experience meaningful differences in efficacy, safety, or immunogenicity when transitioning to the same dose of a biosimilar product [26–28]. To provide evidence relevant to switching patients to LY IGlar from IGlar in clinical practice, we conducted a post hoc analysis of data from Chinese patients included in the randomized phase III T1DM ABES trial who were receiving pre-study IGlar.

METHODS

Study Design

This was a post hoc analysis of a randomized, open-label, 24-week, phase III trial conducted at 20 centers in China (NCT03338023), which has been reported in detail previously [22]. The study was performed in accordance with the 1964 Declaration of Helsinki and its amendments, Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Council for Harmonisation Good Clinical Practice Guidelines, and applicable laws and regulations. The protocol was approved by institutional review boards at each site before study initiation (Table S2 in the electronic supplementary material). All patients provided written informed consent.

Eligible patients had T1DM of duration at least 1 year, glycated hemoglobin (HbA1c) less than 11%, and had been receiving basal-bolus insulins or premixed insulins for at least 90 days at screening. Patients were excluded if they had body mass index greater than 35 kg/m^2; exposure to an IGlar other than Lantus in the previous 30 days; severe hypoglycemia, diabetic ketoacidosis, or emergency room visits for uncontrolled diabetes leading to hospitalization in the previous 6 months; excessive insulin resistance (total daily insulin dose of 1.5 U/kg or higher); or twice-daily IGlar use in the previous 6 months.

Patients were randomized (1:1) to receive either LY IGlar or IGlar delivered using a KwikPen® injector, each given once-daily (QD), plus mealtime insulin lispro injections (bolus insulin). For patients receiving IGlar at screening, the daily starting dose of LY IGlar or IGlar was the same as the pre-study basal insulin dose. Mealtime bolus insulin was administered at the same dose as the pre-study mealtime insulin, based on unit-to-unit conversion. During the study, investigators guided the adjustment of insulin doses based on self-monitored blood glucose (SMBG) data to achieve preprandial blood glucose targets of 79–126 mg/dL (4.4–7.0 mmol/L) while minimizing hypoglycemia.

Assessments

Patients were followed up at clinic visits at weeks 0 (randomization), 2, 4, 6, 12, 18, and 24, and at a safety follow-up visit 4 weeks after the end of study treatment (Fig. S1 in the electronic supplementary material). Patients collected SMBG data at seven time points (at premeal and post-meal at breakfast and lunch, premeal at dinner, bedtime, and 3 A.M.) on two separate days in the week before each visit or at early discontinuation. Patients were provided with ACCU-CHEK® Performa Meters (Roche Diagnostics, Mannheim, Germany) as part of the study.

HbA1c assays were conducted at central laboratory (Covance Inc., Shanghai, China) using a high-performance liquid chromatography system (Variant II, Bio-Rad Laboratories, Inc., Hercules, CA, USA). Immunogenicity was centrally assessed using a proprietary radioligand binding assay with an analytic antibody that binds to anti-LY IGlar, anti-IGlar, and anti-human insulin antibodies (WuXi AppTec Co., Ltd, Shanghai, China). The sensitivity of the assay (11.54 ng/mL) was well within the US Food and Drug Administration's recommended minimum sensitivity of 100 ng/mL [29, 30]. An antibody concentration of 100 ng/mL was shown to be equivalent to around 5% binding during assay validation. On the basis of detection of anti-insulin antibodies using a radioligand binding assay following method validation, conducted at Wuxi lab (WuXi AppTec Co., Ltd., Shanghai, China), a treatment-emergent antibody response (TEAR) was defined as (i) conversion from no detectable antibodies at baseline to detectable antibodies post-baseline; or (ii) an increase of at least 147% in anti-insulin antibody percentage binding from baseline to post-baseline.

Investigators assessed treatment-emergent adverse events (TEAEs), defined as new or worsening events after randomization, which

Table 1 Baseline demographics and characteristics

Variable[a]	LY IGlar (n = 104)	IGlar (n = 106)	Total (N = 210)
Age, years	41.8 (14.9)	41.8 (13.6)	41.8 (14.2)
Males, n (%)	46 (44.2)	50 (47.2)	96 (45.7)
Weight, kg	58.9 (9.5)	59.7 (8.4)	59.3 (9.0)
BMI, kg/m^2	22.0 (2.6)	22.2 (2.3)	22.1 (2.5)
Duration of diabetes, years	10.9 (10.2)	10.5 (9.4)	10.7 (9.8)
Baseline HbA1c, %	7.87 (1.32)	7.85 (1.42)	7.86 (1.37)
Baseline insulin dose			
Total, U/day	42.0 (13.8)	41.5 (11.3)	41.7 (12.5)
Total, U/day/kg	0.71 (0.21)	0.70 (0.17)	0.71 (0.19)
Basal, U/day	14.8 (5.8)	15.5 (5.4)	15.2 (5.6)
Basal, U/day/kg	0.25 (0.09)	0.26 (0.08)	0.26 (0.09)
Bolus, U/day	27.1 (10.3)	26.1 (8.5)	26.6 (9.4)
Bolus, U/day/kg	0.46 (0.16)	0.44 (0.14)	0.45 (0.15)

BMI body mass index, *HbA1c* glycated hemoglobin, *IGlar* insulin glargine, *LY IGlar* LY2963016 insulin glargine, *SD* standard deviation

[a]Values are presented as mean (SD) unless otherwise stated

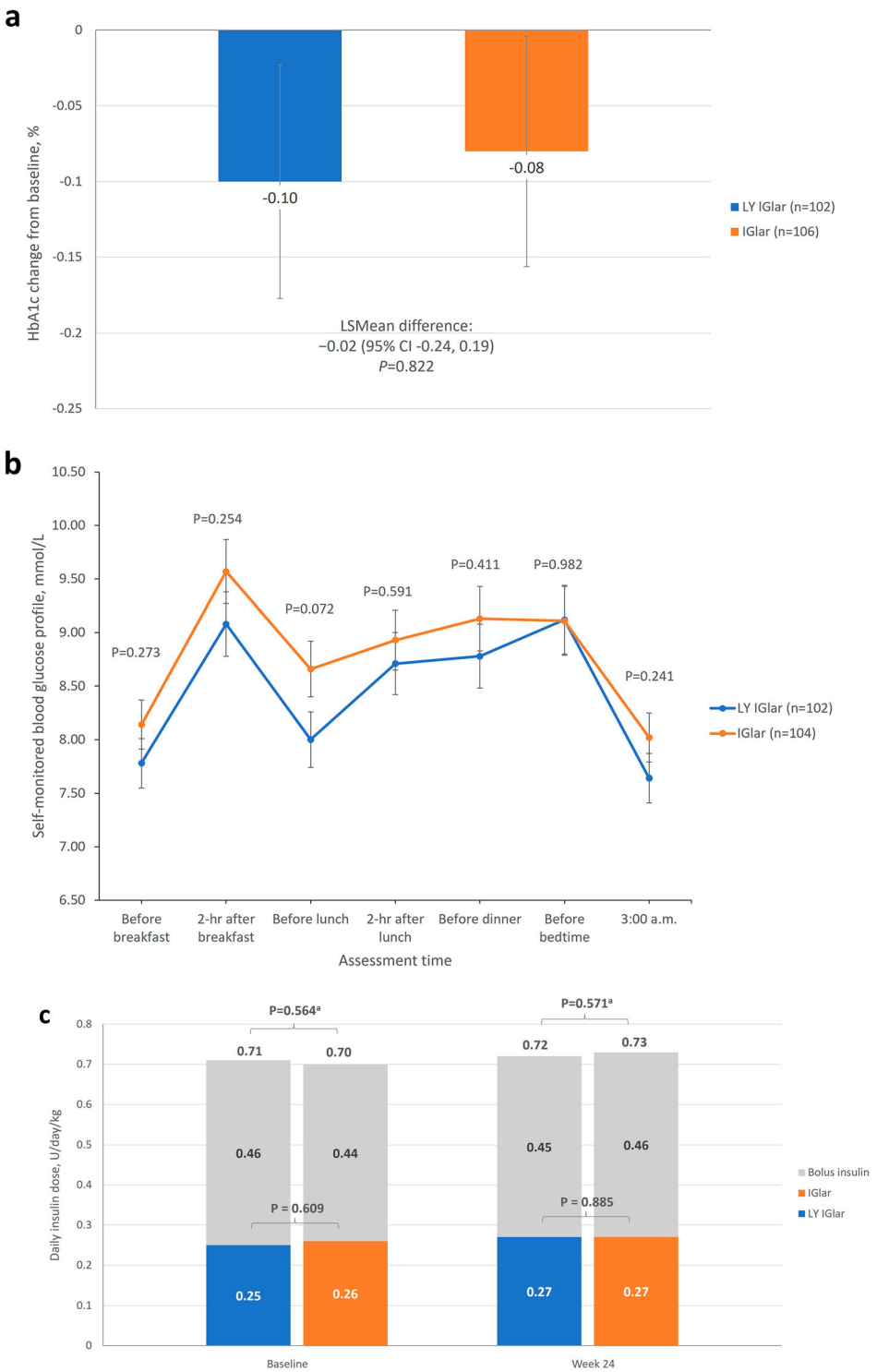


Fig. 1 **a** LSMean (± SE) change in HbA1c from baseline to week 24, **b** LSMean (± SE) seven-point SMBG profile at week 24, **c** LSMean daily total, basal, and bolus insulin doses at week 24. Analyses are based on MMRM. *CI* confidence interval, *IGlar* Lantus®, *LY IGlar* LY2963016, *LSMean* least-squares mean, *MMRM* mixed model for repeated measures, *SE* standard error, *SMBG* self-monitored blood glucose. [a]*P* values refer to comparison of total daily insulin doses

were coded according to the Medical Dictionary for Regulatory Activities, version 22.1. Hypoglycemia was defined as blood glucose level less than 54 mg/dL or 70 mg/dL or less. Severe hypoglycemia was defined as hypoglycemia requiring assistance of another person to administer carbohydrate, glucagon, or take other resuscitative actions. If blood glucose measurements during such an event were unavailable, neurologic recovery following normalization of blood glucose supported attribution of the event as hypoglycemia. Nocturnal hypoglycemia was defined as hypoglycemia events occurring between bedtime and waking.

Statistical Analysis

A post hoc analysis was conducted to evaluate the efficacy and safety of LY IGlar vs. IGlar in the subgroup of patients who were receiving IGlar at screening. Analyses were based on the full analysis set, defined as all randomized patients who received at least one dose of study medication.

Change in HbA1c was analyzed using a mixed model for repeated measures (MMRM), which assumes that missing data occurs at random. The model included change from baseline as the dependent variable; treatment (LY IGlar or IGlar), pre-study metformin or acarbose use, time, and treatment-by-time interaction as fixed effects; baseline value as a covariate; and patient as a random effect. An unstructured variance–covariance matrix was employed. SMBG measurements and daily insulin doses were analyzed using the same MMRM, except that baseline HbA1c was included as a covariate.

HbA1c target attainment (less than 7.0% or at most 6.5%), the proportions of patients with detectable anti-insulin antibodies or TEAR, and percentage antibody insulin binding were analyzed at each visit, overall (i.e., across all visits) and/or at study endpoint using last observation

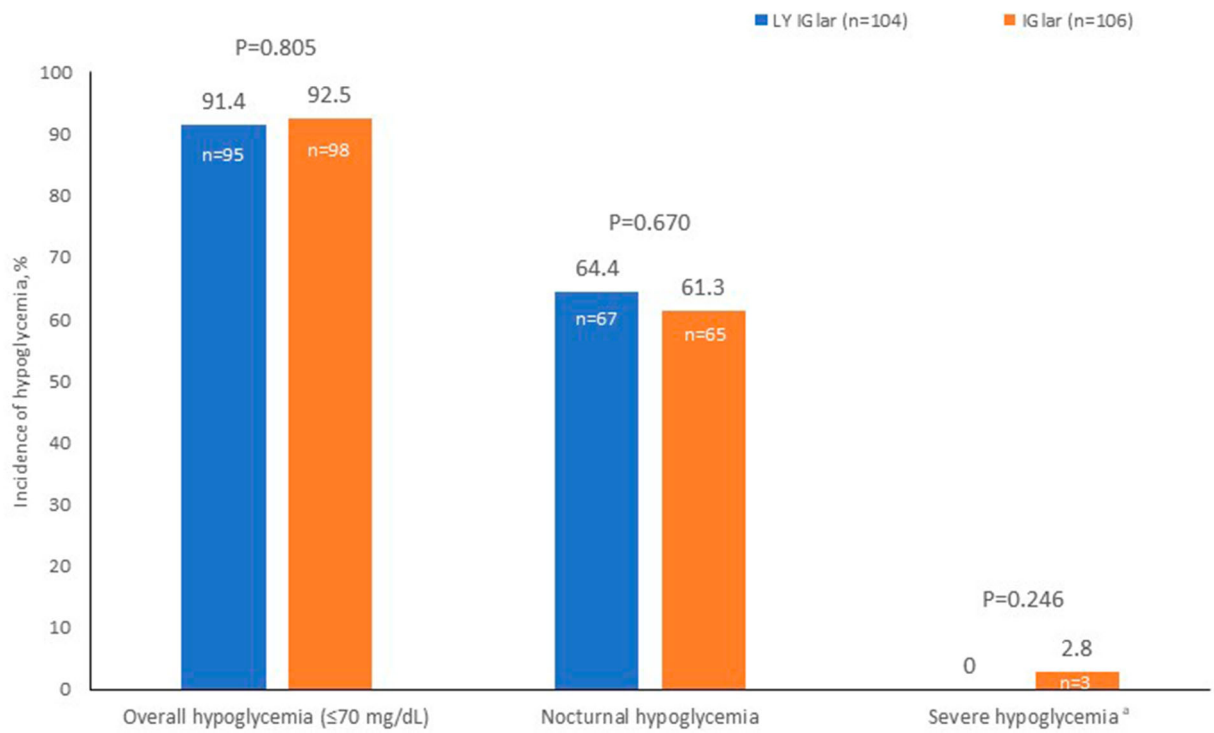


Fig. 2 Incidence of total hypoglycemia (blood glucose level 70 mg/mL or less), nocturnal hypoglycemia, and severe hypoglycemia during the study. *P* values were calculated using Fisher's exact test. [a]Events requiring assistance of another person to administer carbohydrates, glucagon, or resuscitative actions

Table 2 Summary of adverse events

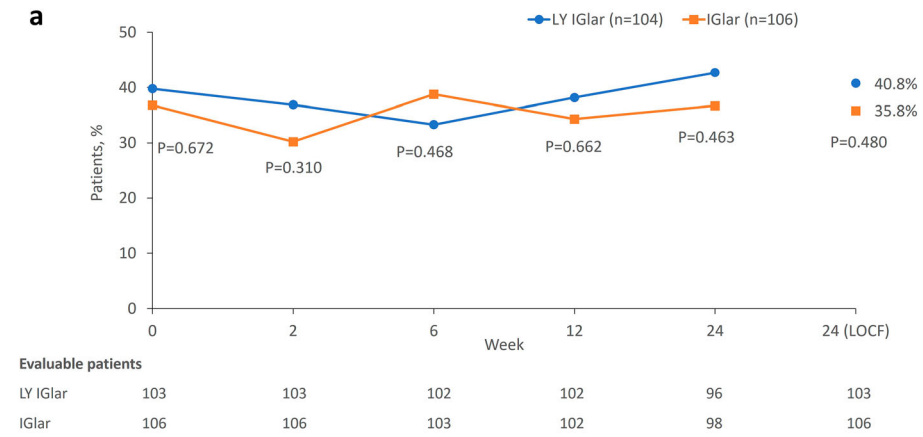
AEs, *n* (%)	LY IGlar (*n* = 104)	IGlar (*n* = 106)	*P* value[a]
Patients with ≥ 1 TEAE	78 (75.0)	71 (67.0)	0.226
TEAEs related to study drug	9 (8.7)	16 (15.1)	0.201
Patients with ≥ 1 SAE	7 (6.7)	8 (7.5)	> 0.999
SAEs related to study drug	2 (1.9)	3 (2.8)	> 0.999
SAEs occurring in > 1 patient			
Hypoglycemia	1 (1.0)	3 (2.8)	0.621
Diabetic ketoacidosis	1 (1.0)	1 (0.9)	> 0.999
Gastroenteritis	1 (1.0)	1 (0.9)	> 0.999
Pneumonia	0 (0.0)	2 (1.9)	0.498
Ureterolithiasis	1 (1.0)	1 (0.9)	> 0.999
Coronary artery disease	1 (1.0)	0 (0.0)	0.495
Diabetic gastroenteropathy	1 (1.0)	0 (0.0)	0.495
Diabetic neuropathy	1 (1.0)	0 (0.0)	0.495
Diabetic retinopathy	1 (1.0)	0 (0.0)	0.495
Gastrointestinal hemorrhage	1 (1.0)	0 (0.0)	0.495
Nephritis	0 (0.0)	1 (0.9)	> 0.999
Ovarian disorder[a]	1 (1.7)	0 (0.0)	> 0.999
Perinephritis	0 (0.0)	1 (0.9)	> 0.999
Pulmonary tuberculosis	1 (1.0)	0 (0.0)	0.495
Spinal fracture	0 (0.0)	1 (0.9)	> 0.999
Tonsillitis	1 (1.0)	0 (0.0)	0.495
Urinary tract infection	0 (0.0)	1 (0.9)	> 0.999
Injection site AEs during treatment	4 (3.8)	4 (3.8)	> 0.999
Special topic assessment[b]	10 (9.6)	5 (4.7)	0.190

AE adverse event, *IGlar* insulin glargine, *LY IGlar* LY2963016 insulin glargine, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

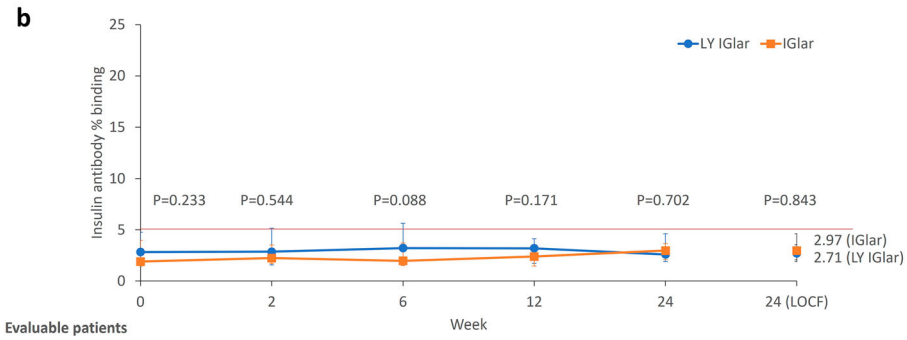
[a]Calculated using Fisher's exact test

[b]Allergic reactions and injection site events

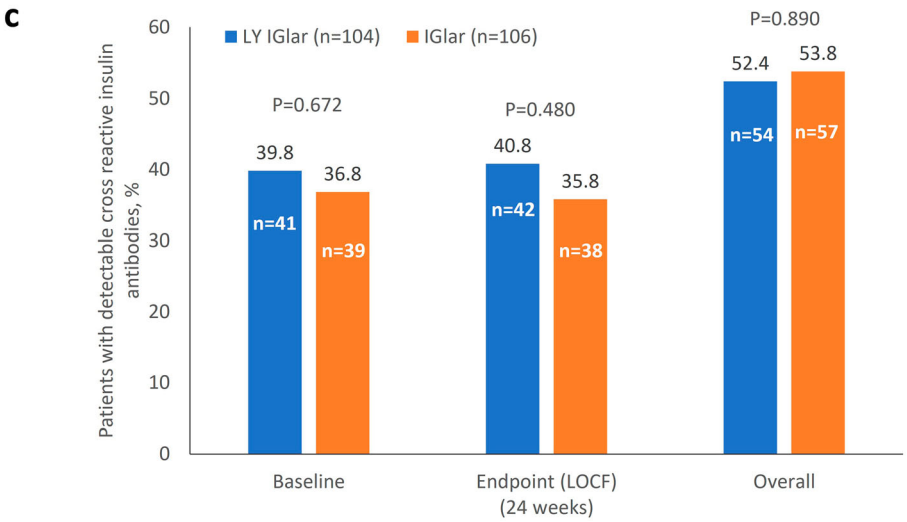
carried forward (LOCF) methodology. Categorical variables were compared by Fisher's exact test or Pearson's chi-squared test. Percentage antibody binding was compared using Wilcoxon's test. The significance level was $P < 0.05$ (two-sided) and tests were not corrected for multiplicity. All analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC, USA).



Evaluable patients						
LY IGlar	103	103	102	102	96	103
IGlar	106	106	103	102	98	106



Evaluable patients						
LY IGlar	41	38	34	39	41	42
IGlar	39	32	40	35	36	38



◀**Fig. 3** **a** Proportion of patients with detectable anti-insulin antibodies at each visit and at study endpoint (LOCF), **b** median (IQR) percentage antibody binding at each visit and at study endpoint (LOCF), **c** proportion of patients at baseline, at study endpoint (LOCF), and overall (i.e., across all visits) with detectable anti-insulin antibodies, **d** proportion of patients with TEAR at each post-baseline visit and study endpoint (LOCF), **e** proportion of patients with TEAR at study endpoint (LOCF) and overall (i.e., across all visits). The red line in **b** indicates the threshold for clinically relevant binding, as defined by the US FDA. *P* values were derived using Fisher's exact test or Pearson's chi-squared test for categorical variables and Wilcoxon's test for percentage antibody binding. *FDA* Food and Drug Administration, *IQR* interquartile range, *LOCF* last observation carried forward, *TEAR* treatment-emergent antibody response

RESULTS

Patients

Of 272 patients randomized in the ABES study, 210 (77.2%) were treated with IGlar at screening and were included in this subgroup analysis (LY IGlar, $n = 104$; IGlar, $n = 106$). The remaining 62 patients were receiving pre-study treatment with other basal-bolus insulins ($n = 35$) or premixed insulin ($n = 27$) and were excluded from this analysis [22]. Baseline characteristics of patients were well balanced between treatment groups (Table 1). The mean ± standard deviation (SD) of age was 41.8 ± 14.9 years in the LY IGlar group and 41.8 ± 13.6 years in the IGlar group, and the mean duration of diabetes was 10.9 ± 10.2 years and 10.5 ± 9.4 years, respectively. At baseline, the mean HbA1c level was 7.87 ± 1.32% and 7.85 ± 1.42%, and mean total daily basal insulin dose was 0.71 ± 0.21 U/day/kg and 0.70 ± 0.17 U/day/kg in the LY IGlar and IGlar groups, respectively.

Efficacy

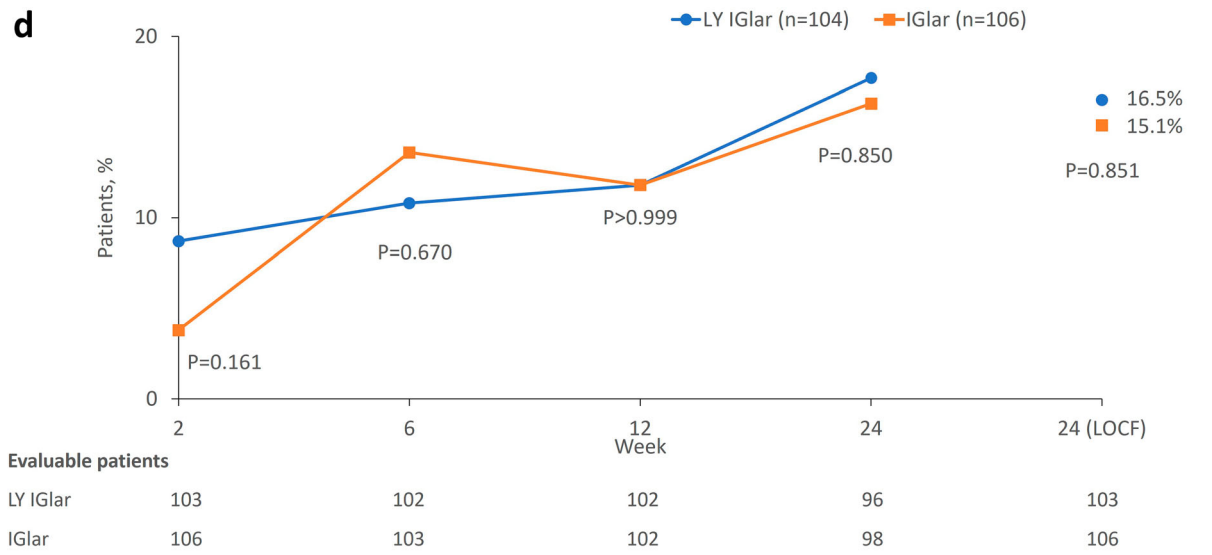
In patients receiving IGlar pre-study, the least-squares mean (LSMean) change from baseline HbA1c at week 24 was comparable in the LY IGlar group (− 0.10%) and the IGlar group (− 0.08%; LSMean difference [95% confidence interval [CI]] − 0.02% [− 0.24, 0.19]; $P = 0.822$) (Fig. 1a). At study endpoint (LOCF), similar proportions of patients in the LY IGlar and IGlar groups achieved HbA1c targets of less than 7.0% (26.5% vs. 32.1%; $P = 0.447$) and 6.5% or less (16.7% vs. 20.8%; $P = 0.482$). The mean SMBG profiles at week 24 for each treatment group are shown in Fig. 1b. No significant treatment differences in LSMean blood glucose levels were observed at any of the seven SMBG profile time points assessed. Furthermore, LSMean ± standard error (SE) values of fasting blood glucose levels at week 24 were similar between the LY IGlar and IGlar groups (140.1 ± 4.2 vs. 146.6 ± 4.2 mg/dL, $P = 0.273$).

At week 24, there was no significant difference between the LY IGlar and IGlar groups in LSMean total basal insulin dose (0.72 vs. 0.73 U/day/kg; $P = 0.571$). Furthermore, increases in total insulin dose during the study were small and comparable between the LY IGlar and IGlar groups (0.02 U/day/kg in both groups) and similar doses of bolus insulin (0.45 vs. 0.46 U/day/kg; $P = 0.410$) and basal insulin (0.27 U/day/kg in both groups; $P = 0.885$) were observed at week 24 (Fig. 1c).

Safety

Among patients receiving IGlar pre-study, in the overall treatment period, the incidence of total hypoglycemia (blood glucose level 70 mg/dL or less, 91.4% vs. 92.5%; blood glucose level less than 54 mg/dL, 54.8% vs. 62.3%) and nocturnal hypoglycemia (64.4% vs. 61.3%) was similar between patients receiving LY IGlar and IGlar during the study (Fig. 2). The incidence of severe hypoglycemia was very low (0.0% vs. 3.0%) and no significant treatment differences were observed between groups.

The incidences of TEAEs and serious adverse events (SAEs) were similar between both treatment groups (Table 2). A low and comparable proportion of patients experienced at least one SAE in both treatment groups, and SAEs were predominantly considered unrelated to study treatment. There were no deaths or



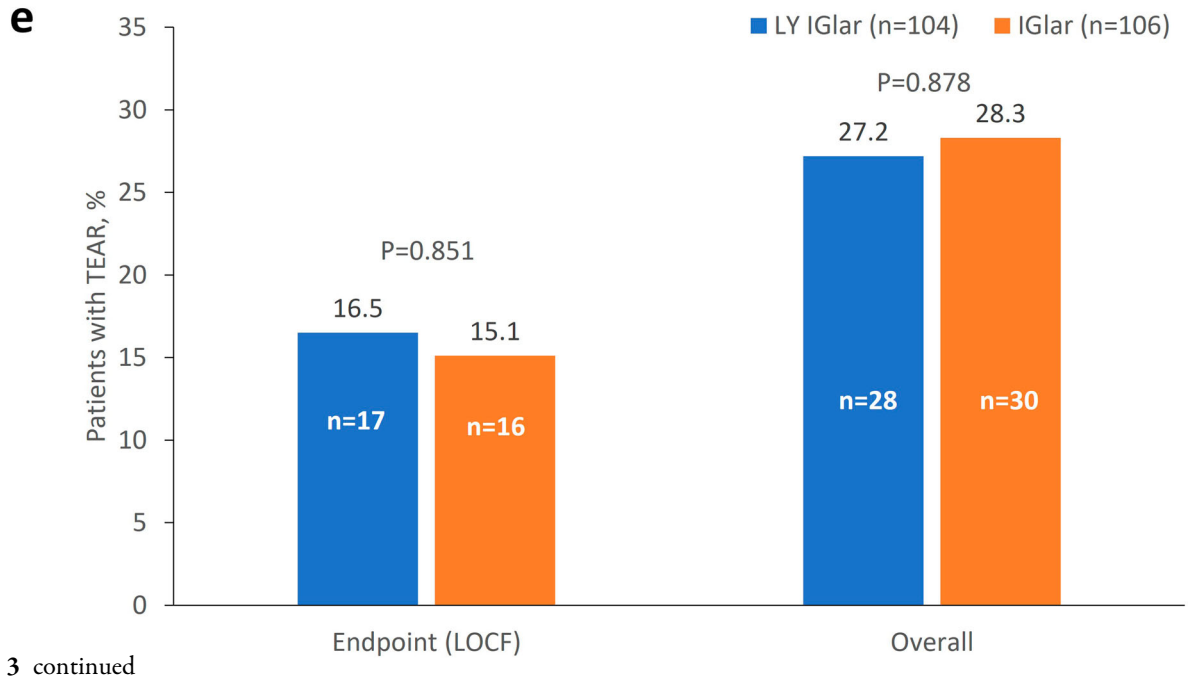


Fig. 3 continued

discontinuations due to adverse events (AEs) during the study. The frequency of TEAEs and treatment-related TEAEs was comparable between the LY IGlar and IGlar groups. Similarly, the rates of injection site reactions and allergic reactions were low and showed no significant difference between groups.

Immunogenicity assessments are displayed in Fig. 3. The proportion of patients with anti-insulin antibodies was similar between the LY IGlar and IGlar groups at baseline, at each post-baseline visit, overall (i.e., across all visits), and at study endpoint (LOCF) (Fig. 3a). Percentage insulin antibody binding was not significantly different between groups and the

median value remained well below the threshold for anti-insulin antibody levels (5% binding) at all visits and at study endpoint (LOCF) (Fig. 3b). The proportion of patients with detectable anti-insulin antibodies was comparable at study endpoint (LOCF) and overall (Fig. 3c), and the proportion of patients with TEAR at each post-baseline visit and at study endpoint (LOCF) was similar between the LY IGlar and IGlar groups (Fig. 3d, e).

DISCUSSION

Insulin replacement therapy is an essential component of the management of T1DM and biosimilar insulins can enhance accessibility to insulin therapy [1, 13]. The present post hoc analysis of the randomized phase III ABES study demonstrated similar efficacy, safety, and immunogenicity outcomes with LY IGlar compared with IGlar over 24 weeks in Chinese patients with T1DM who were receiving daily IGlar plus mealtime insulins pre-study. Glycemic outcomes, including change in HbA1c from baseline and HbA1c target attainment, were similar between the LY IGlar and IGlar groups at week 24, as were total and basal insulin doses. There were no significant differences in the incidence of total, severe, or nocturnal hypoglycemia, and TEAEs were comparable between groups. Immunogenicity outcomes were also comparable for patients receiving LY IGlar and IGlar, with similar rates of insulin antibodies and TEAR observed at study endpoint and overall, and median percentage antibody binding remained well below the threshold for anti-insulin antibody levels (5% binding) in both groups throughout the study.

Regulatory approval of biosimilar medications requires demonstration of a high degree of similarity to the reference product in terms of physicochemical and biologic properties, as well as pharmacologic characteristics, efficacy, and safety in clinical trials [12]. However, the studies designed to support regulatory approval of biosimilar medications do not necessarily address interchangeability, which is a related attribute referring to the ability to switch between two equivalent medications with anticipation of the same effect in a given clinical setting [26]. Although regulatory definitions of interchangeability differ among countries, supportive evidence generally requires evaluation of efficacy, safety, and immunogenicity outcomes when patients are switched between the originator and biosimilar product [26–28]. To our knowledge, the present analysis is the first to provide evidence to support switching from IGlar to LY IGlar in clinical practice in Chinese patients with T1DM. The absence of significant differences between LY IGlar and IGlar is consistent with a recent systematic literature review of 178 studies, in which the authors found no evidence for major efficacy, safety, or immunogenicity concerns when patients are switched to biosimilar from originator biologic medicines [27].

Our findings are consistent with similar subgroup analyses of international, randomized phase III trials comparing LY IGlar with IGlar [24, 31]. In the ELEMENT-1 trial in predominantly Western patients with T1DM, 84.5% of patients reported pre-study IGlar use at baseline [31]. This subgroup of pre-treated patients showed no significant differences in glycemic control, insulin doses, hypoglycemia events, AEs, or immunogenicity outcome measures between patients receiving LY IGlar and IGlar. Furthermore, LY IGlar was shown to be non-inferior to IGlar for change in HbA1c among patients who had received previous treatment with IGlar in a prespecified analysis of the phase III ELEMENT-5 study [24, 31]. Together with the results of sub-analyses of the ELEMENT-1, -2, and -5 studies in patients pre-treated with IGlar [24, 31], our results provide reassurance for clinicians that similar outcomes are expected following switching from IGlar to LY IGlar in patients with T1DM.

The present analysis is limited by its post hoc nature. The ABES trial was not primarily designed to evaluate switching from LY IGlar to IGlar, which may have limited the statistical power to detect treatment differences in the IGlar-pretreated subgroup. The study also had a relatively short 24-week duration, in contrast to similar previous studies with a 52-week duration. This may limit the extrapolation of the

findings of this study past 24 weeks. However, the results of our analysis are consistent with subgroup analyses of the ELEMENT-1 and ELEMENT-2 studies, which showed equivalence of LY IGlar and IGlar at 24 and 52 weeks in patients with T1DM and T2DM who received pre-study IGlar [26]. Furthermore, these data do not address the efficacy and safety of the reverse switch (i.e., from LY IGlar to IGlar). Finally, as the Chinese phase III ABET trial of LY IGlar in patients with T2DM enrolled only insulin-naive patients [23], it was not possible to conduct a corresponding analysis for patients with T2DM.

CONCLUSIONS

In this subgroup analysis of the randomized controlled phase III ABES trial, LY IGlar and IGlar had similar efficacy, safety, and immunogenicity over 24 weeks in Chinese patients with T1DM who were receiving pre-study IGlar. These data support switching from IGlar to LY IGlar in patients with T1DM in clinical practice.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding authors on reasonable request.

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