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Immunogenicity of LY2963016 insulin glargine and Lantus® insulin glargine in Chinese patients with type 1 or type 2 diabetes mellitus

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Abstract

Aims: To evaluate the immunogenicity of LY2963016 insulin glargine (LY IGlar) versus originator insulin glargine (IGlar [Lantus®]) in Chinese patients with type 1 (T1DM) or type 2 diabetes mellitus (T2DM).

Materials and Methods: ABES and ABET were prospective, randomized, active control, open-label, phase III studies, which enrolled Chinese patients with T1DM ($N = 272$) and T2DM ($N = 536$), respectively. Using data from these trials, immunogenicity of LY IGlar and IGlar was evaluated by comparing the proportion of patients with detectable anti-insulin glargine antibodies and the median antibody levels (percent binding) between the treatment groups. The incidence of anti-insulin antibodies and treatment-emergent antibody response (TEAR) were compared using Fisher's exact test or Pearson's chi-squared test. Levels of anti-insulin antibodies were compared using the Wilcoxon rank-sum test. We also evaluated the relationship between antibody formation or TEAR and clinical outcomes using analysis of covariance, negative binomial regression, or partial correlations.

Results: There were no significant treatment differences in the incidence of detectable anti-insulin antibodies, median antibody levels or TEAR, overall or at Week 24 with last observation carried forward, and median antibody levels were low (<5%) after 24 weeks of treatment, in patients with T1DM or T2DM. Levels of anti-insulin antibodies and development of TEAR were not associated with efficacy (glycated haemoglobin, insulin dose [U/kg/d] and hypoglycaemia) or safety outcomes.

Conclusions: The immunogenicity profiles of LY IGlar and IGlar are similar, with low levels of anti-insulin antibodies observed for both insulins. No association was observed between antibody levels or TEAR status and clinical outcomes.

KEYWORDS
biosimilar insulin, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Injectable exogenous basal insulin is an important component of antihyperglycaemic treatment for patients with type 1 (T1DM) and type 2 diabetes mellitus (T2DM).[1,2] Insulin glargine (IGlar; Lantus® [Sanofi-Aventis, Paris, France]) is a long-acting basal insulin analogue, developed using recombinant DNA technology, and was the first long-acting insulin analogue to receive regulatory approval, in 2000.[3,4] LY2963016 insulin glargine (LY IGlar; Abasaglar [European Union]; Basaglar [United States]) has a primary amino acid sequence, pharmaceutical form and strength identical to reference IGlar.[5] LY IGlar was the first biosimilar insulin to receive approval from the European Medicines Agency (EMA) in September 2014[5,6] and received approval from the US Food and Drug Administration (FDA) in December 2015.[7] LY IGLar has shown similar efficacy and safety to IGlar in patients with T1DM and T2DM across multiple randomized, phase III noninferiority trials, in both Western and Asian patient populations.[5,8-11]

Biologic drugs such as insulin analogues are produced using living cell cultures and have inherent manufacturing variability that can result in subtle differences in immune responses and clinical effects between batches of the same drug and between biosimilar and originator biologics.[12] The EMA, FDA and China National Medical Products Administration therefore require that a proposed biosimilar demonstrates similarity to the "originator" or "reference" biologic drug in terms of quality characteristics, biological activity, safety and efficacy.[13-16] In particular, the comprehensive safety evaluation requirements include evaluation of immunogenic potential. In this regard, LY IGlar and IGlar exhibited comparable immunogenicity profiles in Western patients with T1DM and T2DM in the global, randomized, phase III ELEMENT-1 and -2 trials.[8,9]

The immunogenic potential of a biopharmaceutical depends on a variety of factors related to the product and the patient.[17-19] Patient-specific factors that may affect immunogenicity include immunological status (ie, immunocompetent vs. immunosuppressed status), prior sensitization, allergy, route of administration, human leukocyte antigen (HLA) haplotypes, genetic polymorphisms in cytokine genes, quantity or quality of endogenous protein, and preexisting antibodies.[20,21] Ethnic factors can affect a drug's efficacy and safety,[22,23] which in turn may potentially affect immunogenicity. The immunogenicity results of insulin glargine, including Lantus® and biosimilars, have been investigated in the ELEMENT-1 and 2 trials, which mainly enrolled White patients (ELEMENT-1, White participants 74.5%; ELEMENT-2, White participants 78.4%).[24] It is estimated that the number of adults with diabetes in China exceeded 140 million in 2021, ranking first in the world.[25] However, there have been no reported studies on the immunogenicity of IGlar or LY IGlar in East Asian populations. Considering the huge number of patients with diabetes in China, the immunogenicity results of insulin glargine in a Chinese population, including its association with clinical outcomes, would therefore be highly informative.

The efficacy and safety of LY IGlar and IGlar has been investigated in Chinese patients with T1DM and T2DM in the randomized, open-label phase III ABES and ABET trials, respectively.[5,10] In ABES, adult patients with T1DM received LY IGlar or IGlar in combination with premeal insulin lispro and immunogenicity was evaluated throughout the 24-week treatment period.[10] In ABET, insulin-naïve adult patients with T2DM were assigned to receive LY IGlar or IGlar in combination with ≥2 oral antihyperglycaemic medications, and immunogenicity was evaluated over 24 weeks.[5] However, the primary ABES and ABET study publications mainly focused on efficacy and safety. An accurate immunogenicity profile of LY IGlar and IGlar in a Chinese population could provide physicians with information about the potential of insulin antibody development.

Here, we present a comprehensive analysis of the immunogenicity profiles of LY IGlar and IGlar using data collected during the ABES and ABET trials. We evaluated anti-insulin antibody levels, cross-reactive insulin antibody levels and the proportion of patients with a treatment-emergent antibody response (TEAR) during the 24-week treatment period, as well as the association between insulin antibodies or TEAR and clinical outcomes in Chinese patients with T1DM and T2DM.

2 | METHODS

2.1 | Study design and patients

ABES and ABET were prospective, randomized, active control, open-label, 24-week treatment, phase III studies that enrolled Chinese patients with T1DM and T2DM, respectively. In ABES, adult patients with T1DM received LY IGlar or IGlar in combination with premeal insulin lispro for 24 weeks.[10] In ABET, insulin-naïve patients with T2DM received LY IGlar or IGlar once daily for 24 weeks at a starting dose of 10 U/d, followed by a weekly dosing algorithm and a fixed dose of ≥2 oral antihyperglycaemic medications.[5]

The present analysis included all randomized patients from the ABES (T1DM, $N = 272$; LY IGlar, $n = 137$; IGlar, $n = 135$) and ABET (T2DM, $N = 536$; LY IGlar, $n = 359$; IGlar, $n = 177$) studies who received ≥1 dose of study medication. Descriptive and inferential analyses were performed in patients with valid antibody testing (detected or not detected) at baseline and with at least one post-baseline visit.

The methods of these trials have been reported in full previously.[5,10] Both of these trials followed the principles outlined in the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki, and the study protocols were registered at ClinicalTrials.gov (ABES: NCT03338023; ABET: NCT03338010). Written, informed consent was obtained from all patients before inclusion in both studies.

2.2 | Measurements

In the ABES and ABET studies, samples for antibody detection were collected at baseline, and during study visits at Weeks 2, 4 (ABET

only), 6 (ABES only), 12 and 24, and measured at a central laboratory (WuXi AppTec Co., Ltd, Shanghai, China) using a proprietary validated radioligand binding assay designed to detect anti-IGlar antibodies in the presence of the investigational product. Anti-LY IGlar antibodies were quantified as percent binding, defined as the percent of the total amount of radiolabelled LY IGlar that coprecipitates with the antibodies. The assay lower limit of detection of total insulin antibodies is 1.19%. The anti-LY IGlar antibody assay has cross-reactivity to IGlar and human insulin, and the same assay was used to detect antibodies to IGlar or insulin. The assay's sensitivity was 11.54 ng/mL using a polyclonal affinity-purified anti-insulin antibody, satisfying the FDA's recommendation that screening assays be sensitive enough to detect clinically relevant antibody concentrations of at least 100 ng/mL.[26,27] An antibody concentration of 100 ng/mL is equivalent to approximately 5% binding during assay validation. Specificity was evaluated using excess unlabelled LY IGlar and cross-reactivity to human insulin was assessed using unlabelled insulin. Further analyses of cross-reactive insulin antibodies (ie, anti-IGlar and anti-insulin) were conducted to confirm that immune responses to LY IGlar and IGlar were similar with respect to anti-human insulin antibodies. The threshold for the cross-reactive insulin antibody assay was a 1.00% binding value.

Treatment-emergent antibody response was defined based on changes in anti-insulin antibody levels (percent binding) from baseline based on the ABES and ABET study protocols. For patients with no detectable insulin antibodies at baseline, a treatment-induced TEAR was defined as detection of anti-insulin antibodies post baseline. For patients with detectable anti-insulin antibodies at baseline, a treatment-boosted TEAR was defined as an increase in anti-insulin antibody level (percent binding) of ≥147% of the baseline value.

2.3 | Statistics

The analysis of insulin antibodies included all randomized patients in the ABES and ABET trials who received ≥1 dose of study medication with valid antibody testing at baseline and ≥1 valid post-baseline measurement. The proportion of patients with detectable anti-insulin antibodies and median antibody levels (percent binding) at all study time points and Week 24 with last observation carried forward (LOCF) were calculated and summarized using descriptive statistics. Differences in the proportion of patients with detectable anti-insulin antibodies and TEARs between treatment groups were compared using Fisher's exact test or Pearson's chi-squared test. Treatment differences in anti-insulin antibody levels were compared using Wilcoxon's rank-sum test.

We also evaluated the association between antibody formation and clinical response to LY IGlar/IGlar as indictated by changes in glycated haemoglobin (HbA1c) level (%), basal insulin dose (U/kg/d) and total hypoglycaemia (adjusted for 1 year, including blood glucose ≤3.9 mmol/L). Only patients with clinical response variable data available at baseline and ≥1 post-baseline measurement were included in each of these analyses. The association between insulin antibodies and clinical outcomes was assessed using scatter plots and analysed using analysis of covariance (ANCOVA) and by partial correlations. A negative binomial regression was used to explore the relationship between insulin antibodies and overall total hypoglycaemia.

A P value <0.05 was considered to indicate a statistically significant difference between groups. All analyses were performed using SAS version 9.4 (SAS, Cary, North Carolina).

3 | RESULTS

3.1 | Patients

Patient demographics and baseline disease characteristics were well balanced between the treatment groups in both the T1DM and T2DM populations (Table S1).[5,10] The mean duration of T1DM or T2DM was more than 10 years. In ABES, most patients (77.2%) were receiving Lantus®-bolus prestudy treatment, while 12.9% and 9.9% of patients were receiving other basal-bolus and premixed insulins, respectively. In ABET, 67.0% patients were receiving two oral antihyperglycaemic medications before randomization and 71.5% patients were receiving sulphonylureas.

Of the 272 patients with T1DM included in the ABES study who received ≥1 dose of study medication, 210 (77.2%) reported prestudy use of IGlar and 35 (12.9%) reported prestudy use of other basal insulins. A total of 270 patients (LY IGlar: $n = 136$; IGlar: $n = 134$) had a baseline test for anti-insulin antibodies and ≥1 post-baseline test, of whom 144 (53.3%) had detectable anti-insulin antibodies during the 24 weeks of treatment.

Of the 536 patients with T2DM in the ABET study who received ≥1 dose of study medication, 534 (LY IGlar: $n = 357$; IGlar: $n = 177$) had a baseline test for anti-insulin antibodies and ≥1 post-baseline test, of whom 100 (18.7%) had detectable antibodies during the 24-week study period.

3.2 | Immunogenicity

3.2.1 | Patients with T1DM included in the ABES study

The overall proportion of patients with detectable anti-insulin antibodies during the 24-week treatment period was similar in the LY IGlar and IGlar groups (55.9% [$n = 76$] vs 50.7% [$n = 68$], respectively; $P = 0.464$). Furthermore, no statistically significant differences in the proportion of patients with detectable anti-insulin antibodies were observed at Weeks 2, 6, 12 or 24, or at endpoint (LOCF) between the LY IGlar and IGlar groups (Figure 1A).

The median anti-insulin antibody levels (percent binding) were low (<5%) in both treatment groups and there were no statistically significant treatment differences other than at Week 6 (LY IGlar: 3.63%; IGlar: 1.96%; $P = 0.030$ [Figure 1B]). At endpoint (LOCF), the median anti-insulin antibody levels (percent binding) in the two groups were similar (LY IGlar: 3.15; IGlar: 2.87; $P = 0.649$).
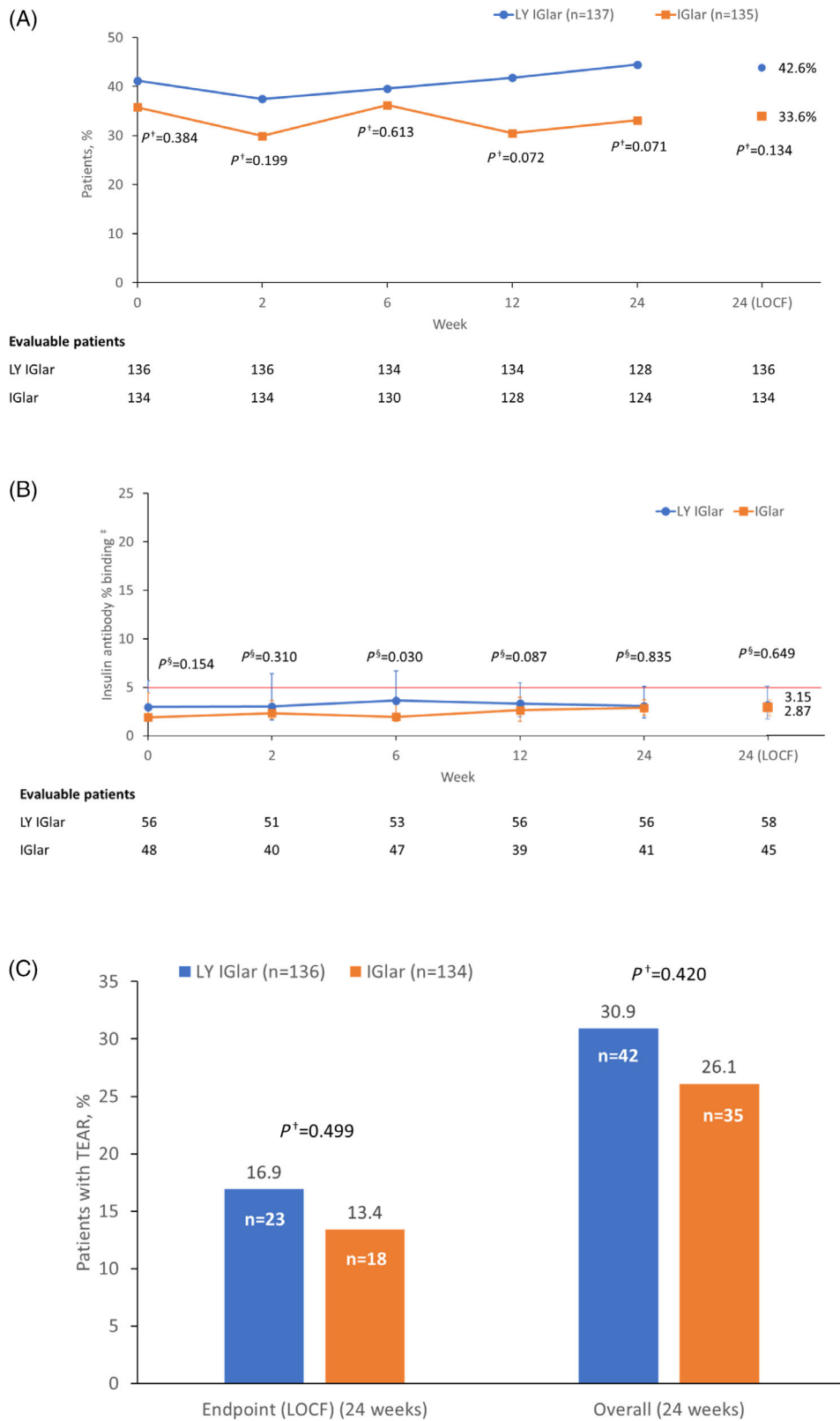
FIGURE 1 Summary of anti-insulin antibodies in patients with type 1 diabetes mellitus. A, Proportion of patients with detectable anti-insulin glargine antibodies. B, Median level of insulin antibodies (percent binding). C, Proportion of patients with a treatment-emergent antibody response (TEAR). Red horizontal line indicates the 5% binding level in the screening assay, which approximately equates to 100 ng/mL. Only patients with valid antibody testing at baseline and ≥1 valid post-baseline measurement were included in the analyses. [†]Treatment differences were tested using Fisher's exact test or Pearson's chi-squared test. [‡]Data are median, and error bars represent the interquartile range (25%, 75%). [§]Treatment differences were tested using Wilcoxon's rank-sum test. IGlar, insulin glargine; LOCF, last observation carried forward; LY IGlar, LY2963016 insulin glargine
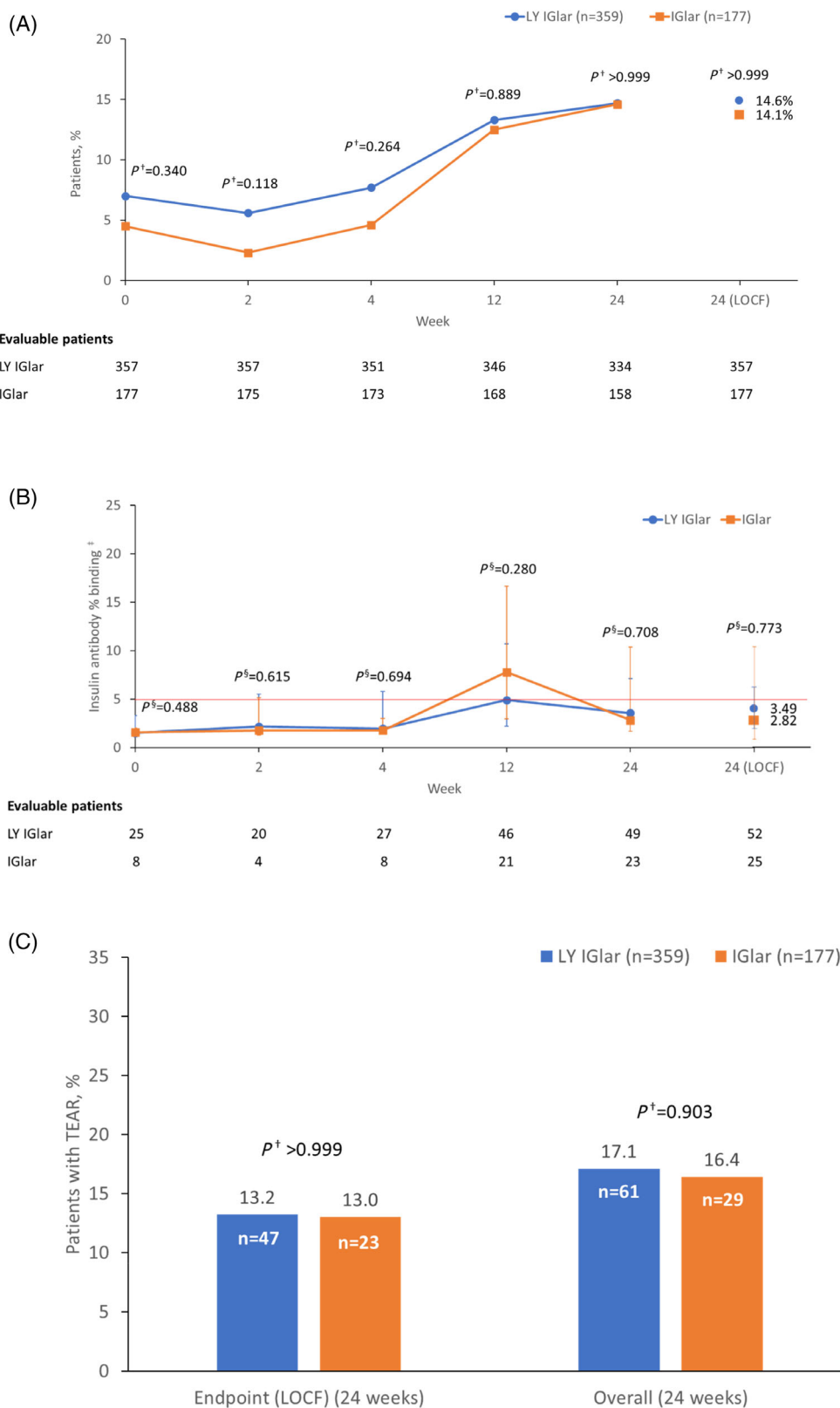
FIGURE 2 Summary of anti-insulin antibodies in patients with type 2 diabetes mellitus. A, Proportion of patients with detectable anti-insulin glargine antibodies. B, Median level of insulin antibodies (percent binding). C, Proportion of patients with a treatment-emergent antibody response (TEAR). Pink horizontal line indicates the 5% binding level in the screening assay, which approximately equates to 100 ng/mL. Only patients with valid antibody testing at baseline and ≥1 valid post-baseline measurement were included in the analyses. [†]Treatment differences were tested using Fisher's exact test or Pearson's chi-squared test. [‡]Data are median, and error bars represent interquartile range (25%, 75%). [§]Treatment differences were tested using Wilcoxon's rank-sum test. IGlar, insulin glargine; LOCF, last observation carried forward; LY IGlar, LY2963016 insulin glargine

The incidence of TEAR was comparable for patients receiving LY IGlar and IGlar at the study endpoint (LOCF; 16.9% vs 13.4%; *P* = 0.499) and overall throughout the 24-week treatment period (30.9% vs 26.1%; *P* = 0.420 [Figure 1C]).

There was no statistically significant treatment difference in the proportion of patients with cross-reactive antibodies, or in median cross-reactive antibody levels, at any study time point or the endpoint (Figures S1A,B). At endpoint (LOCF), the median cross-reactive antibody levels (percent binding) in the LY IGlar and IGlar groups were 3.66% and 2.96% (*P* = 0.546; Table S2).

3.2.2 | Patients with T2DM included in the ABET study

The overall proportion of patients with detectable anti-insulin antibodies during the 24-week treatment period was comparable in the LY IGlar and IGlar treatment groups (19.3% [*n* = 69] vs 17.5% [*n* = 31];

P = 0.639). In addition, the proportion of patients with detectable anti-insulin antibodies at Weeks 2, 4, 12 and 24 and at endpoint (LOCF) was comparable in the LY IGlar and IGlar groups, with no statistically significant differences at any time point (Figure 2A).

Low levels of anti-insulin antibodies (percent binding) in the two treatment groups were observed throughout the study, with median levels <5% except for the IGlar group at Week 12 (Figure 2B). No statistically significant treatment differences were observed at any time point or at the study endpoint (LOCF; LY IGlar: 3.49%; IGlar: 2.82%; *P* = 0.773).

The incidence of TEAR was comparable for patients receiving LY IGlar and those receiving IGlar at the study endpoint (LOCF; 13.2% vs. 13.0%; *P* > 0.999) and overall throughout the 24-week treatment period (17.1% vs. 16.4%; *P* = 0.903 [Figure 2C]). The proportion of patients with cross-reactive antibodies and the median levels of cross-reactive antibodies were comparable in the two treatment groups at all time points and at the study endpoint (Figures S2A,B). At the study endpoint (LOCF), the median cross-reactive antibody levels
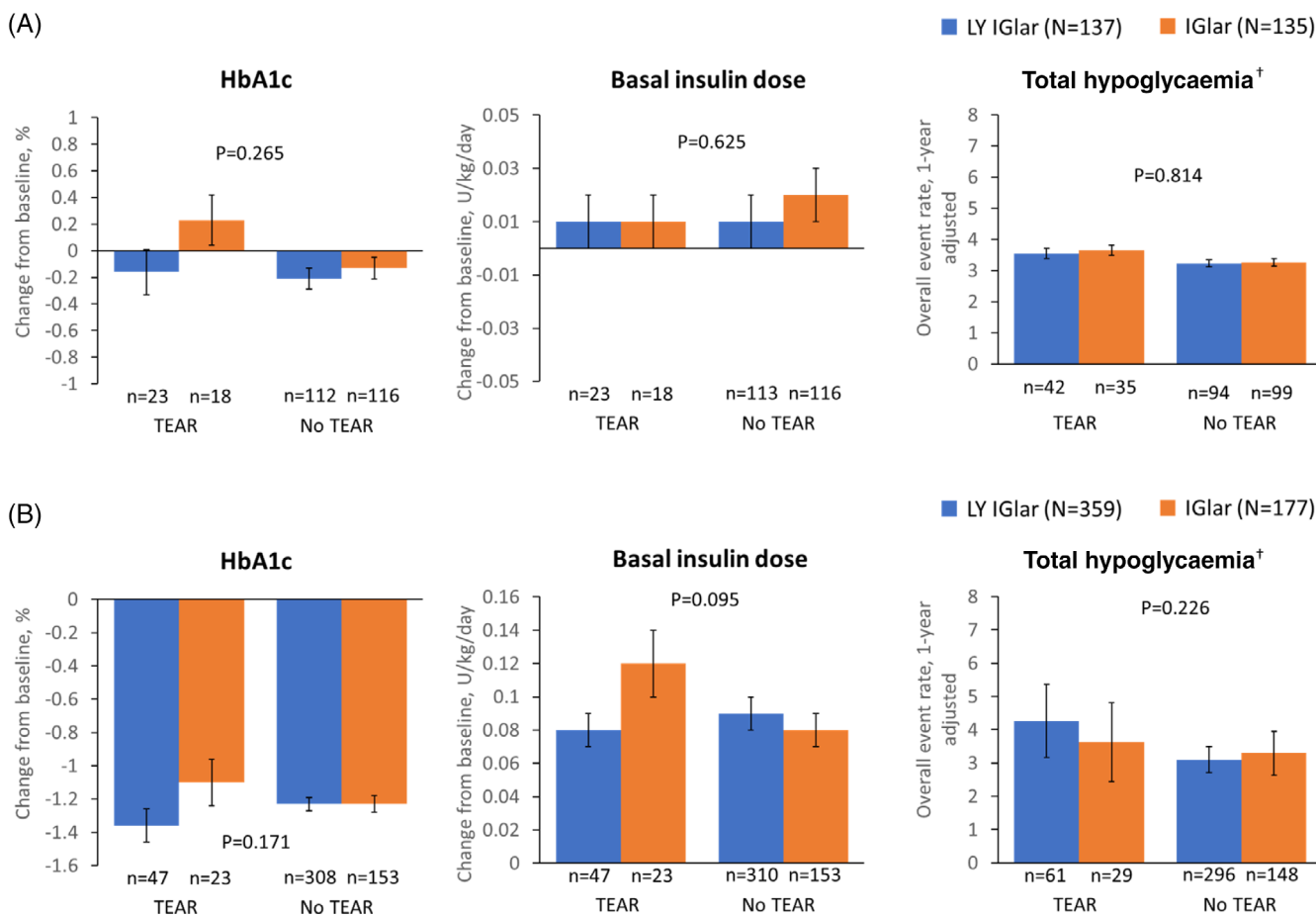

FIGURE 3 Association between treatment-emergent antibody response (TEAR) status and efficacy outcomes (change in HbA1c, basal insulin dose and overall total hypoglycaemia rate adjusted for 1 year) in A, patients with type 1 diabetes mellitus and B, patients with type 2 diabetes mellitus. Data are presented as least squares mean ± standard error change from baseline to LOCF endpoint. *P* values for the interactions between TEAR and glycated haemoglobin (HbA1c) or basal insulin dose were calculated using an analysis of covariance (ANCOVA) model; interaction between TEAR and hypoglycaemia was calculated using a negative binomial model. †Adjusted for 1 year, events with blood glucose ≤3.9 mmol/L included. IGlar, insulin glargine; LOCF, last observation carried forward; LY IGlar, LY2963016 insulin glargine

(percent binding) in the LY IGlar and IGlar groups were 3.94% and 5.12% ($P = 0.646$; Table S2).

3.3 | Association between insulin antibodies and efficacy outcomes

For patients with T1DM, further analyses were performed on the association between TEAR status and least-squares mean change in HbA1c, basal insulin dose (U/kg/d) from baseline to endpoint (LOCF) or overall total hypoglycaemia (adjusted for 1 year). The treatment-by-TEAR interaction was not statistically significant for any of these efficacy outcomes (Figure 3A), indicating no differential treatment effect for patients who did or did not develop a TEAR. A similar result was observed for patients with T2DM, with no statistically significant treatment-by-TEAR interactions observed for change in HbA1c, basal insulin dose (U/kg/d) from baseline to Week 24 (LOCF) or overall total hypoglycaemia (adjusted for 1 year; Figure 3B).

No significant correlation was observed between total insulin antibody levels and efficacy outcomes (HbA1c, basal insulin dose [U/kg/d] or total hypoglycaemia [adjusted for 1 year]) at endpoint (LOCF) in patients with T1DM or T2DM (Figure 4A,B). Similarly, for patients with T1DM and T2DM, there was no significant interaction between detectable antibody levels at endpoint (LOCF) and change from baseline to endpoint (LOCF) in HbA1c ($P = 0.592$ and $P = 0.849$, respectively), basal insulin dose (U/kg/d; $P = 0.794$ and $P = 0.982$, respectively) or between overall detectable antibodies and overall total hypoglycaemia (adjusted for 1 year; $P = 0.212$ and $P = 0.316$ [negative binomial model], respectively).

3.4 | Association between TEAR and safety outcomes

No significant treatment-by-overall TEAR interactions were observed for the occurrence of treatment-emergent adverse events (TEAEs), TEAEs related to study drug, special topic assessment (allergic reactions and injection site events), injection site reactions (pain, pruritus and rash associated with the injection, or for the characteristics of the injection site [abscess, nodule, lipoatrophy, lipohypertrophy or induration]) or serious adverse events in patients with T1DM or T2DM (Table S3). However, for patients with T1DM there were too few events of special topic assessment, injection site reactions or serious adverse events for the interaction test to be performed. Evaluation of adverse events by system organ classes and individual preferred terms in patients with TEAR revealed no clinically significant treatment differences in patients with T1DM or T2DM (Table S4).

4 | DISCUSSION

Long-acting insulin analogues are protein products with complex structures and have the potential to induce immune responses.

Furthermore, minor structural variations between biosimilars and originator biologics can potentially result in differences in immunogenicity, safety and therapeutic efficacy.[28] Regulatory requirements for biosimilar development therefore include comprehensive evaluation of the immunogenicity of a biosimilar medicine compared with the originator drug.[13-16] In this study, we showed that LY IGlar and IGlar have similar immunogenicity profiles in Chinese patients with T1DM or T2DM, with no significant treatment differences overall or at any study time point, including Week 24 with LOCF, in the prevalence of detectable anti-insulin antibodies, median antibody levels (apart from Week 6 in patients with T1DM; LY IGlar: 3.63%; IGlar: 1.96%; $P = 0.030$) or TEAR. Low median antibody levels (below 5%, approximately equivalent to <100 ng/mL) were measured for patients receiving LY IGlar and IGlar at the vast majority of study time points and at the treatment endpoint. Furthermore, levels of anti-insulin antibodies and TEAR were not associated with efficacy or safety outcomes. Overall, these findings in a Chinese patient population are consistent with those reported for the predominantly Western patients included in the ELEMENT-1 and -2 trials, and further support the similar immunogenicity and safety profiles of LY IGlar and IGlar.[29]

In addition to evaluation of the proportion of patients with detectable anti-insulin antibodies and median antibody levels, assessment of changes in antibody status over time is also of high clinical relevance. In this regard, TEAR provides a measure of immune response by indicating changes in a patient's antibody status from baseline. Our results show that a similar proportion of patients receiving LY IGlar and IGlar had a TEAR, in both the T1DM (endpoint [LOCF]; 16.9% vs. 13.4%, respectively; $P = 0.499$) and T2DM (endpoint [LOCF]; 13.2% vs 13.0%, respectively; $P > 0.999$) patient populations. This is consistent with findings in the predominantly Western patients included in the ELEMENT-1 and -2 studies, which also showed a comparable incidence of TEAR for patients with T1DM and T2DM receiving LY IGlar and IGLar.[29]

Patients with T1DM and T2DM are known to have differential immune responses that can influence immunogenicity profiles, with higher levels of anti-insulin antibodies generally observed in patients with T1DM versus those with T2DM.[30,31] In addition, the majority of patients with T1DM will have been using exogenous insulin therapy before entering clinical trials, which is reflected by the high proportion of patients in the ABES trial who had previously used IGlar or other basal insulins (90.1%). Therefore, as would be expected, the baseline presence of detectable anti-insulin antibodies was higher among patients with T1DM in the present study versus the insulin-naïve patients with T2DM. Furthermore, a higher proportion of patients with T1DM had detectable anti-insulin antibodies at all study time points compared with those with T2DM, similar to observations in the ELEMENT-1 and -2 trials.[29] However, the median antibody level was <5% for patients with T1DM and T2DM at almost all study time points and no treatment differences were observed. Interestingly, a lower overall proportion of patients had detectable anti-insulin antibodies at any point during 24 weeks of treatment in the ELEMENT-1 (LY IGlar: 30.2%; IGlar: 33.7%) and ELEMENT-2 (LY IGlar: 15.3%; IGlar: 11.0%) trials compared with the ABES (LY IGlar: 55.9%; IGlar:
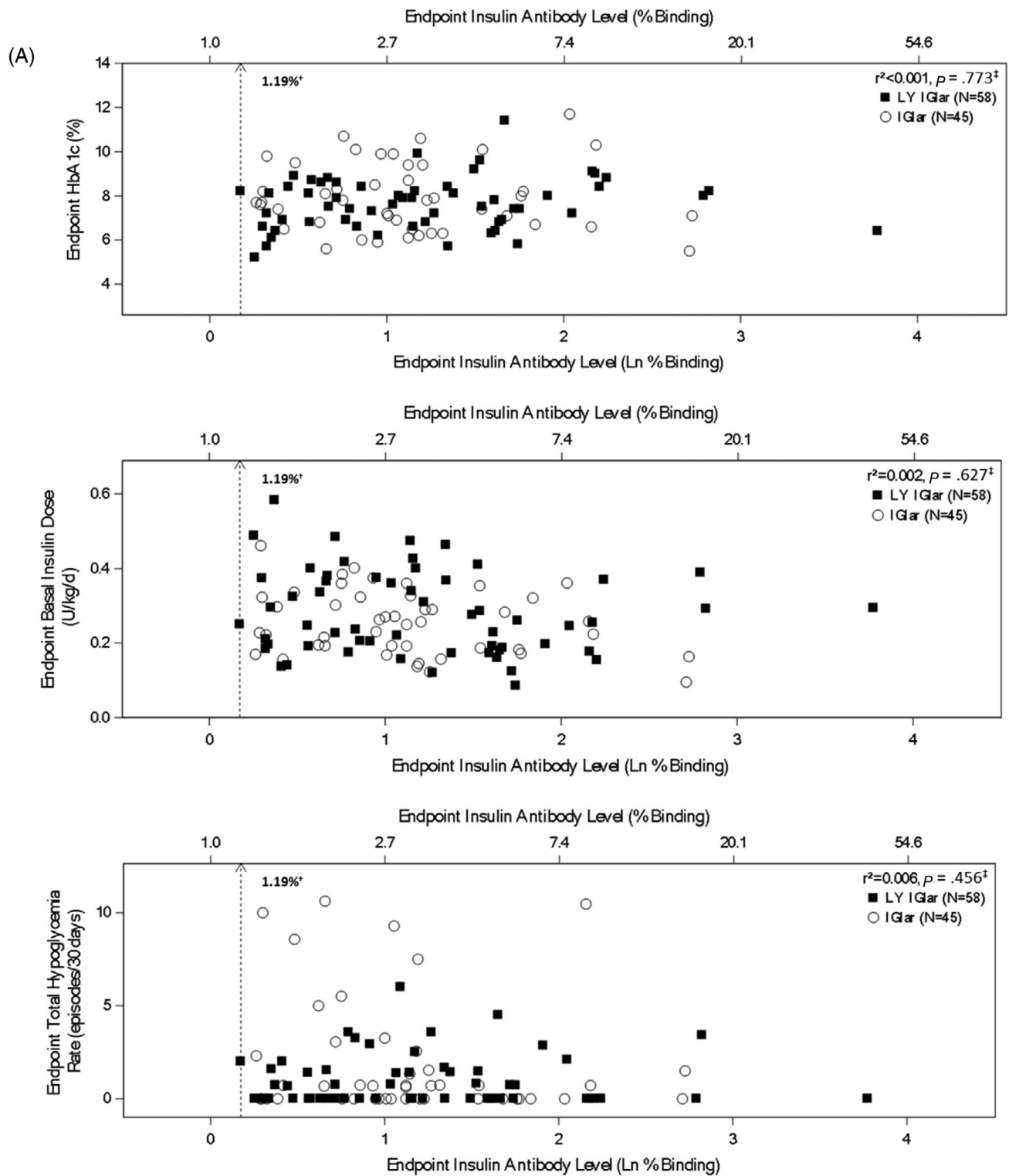
FIGURE 4 Relationship between total insulin antibody levels (percent binding) and efficacy outcomes (glycated haemoglobin [HbA1c], basal insulin dose and total hypoglycaemia rate adjusted for 1 year) at endpoint (Week 24, last observation carried forward [LOCF]) in A, patients with type 1 diabetes mellitus and B, patients with type 2 diabetes mellitus. [†]Quantitative detection limit of the assay. [‡]Partial correlation measures of the relationship between endpoint measures (HbA1c, basal insulin dose or total hypoglycaemia rate) and endpoint antibody level after adjustment for baseline HbA1c, basal insulin at study entry, and prestudy metformin or acarbose usage. Only patients with nonmissing endpoint antibody levels and nonmissing baseline values, and with at least one nonmissing post-baseline value of the response variable, were included in the analysis. IGlar, insulin glargine; LY IGlar, LY2963016 insulin glargine
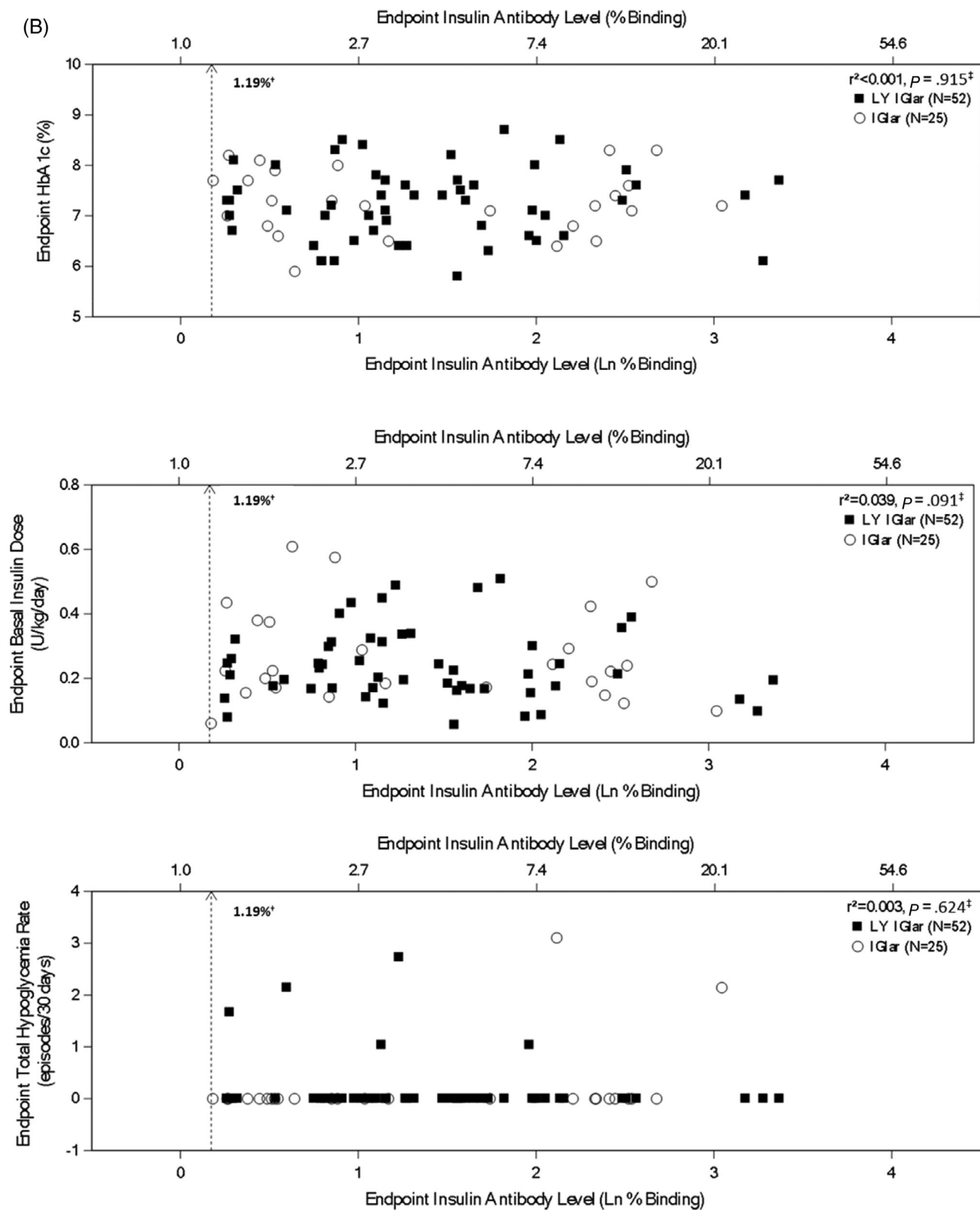
(B)

FIGURE 4 (Continued)

50.7%) and ABET (LY IGlar: 19.3%; IGlar: 17.5%) trials.[29] This may reflect differences between the patient populations. Across-study comparisons of anti-drug antibody incidence should be made with caution because the observed immunogenicity of a compound depends on many factors, including trial design, laboratory factors and patient population.[32] For example, patients with T1DM in the ABES

study had a higher baseline level of anti-insulin antibodies compared with those in ELEMENT-1 (ABES: LY IGlar 2.97% vs. IGlar 1.91%; ELEMENT-1: LY IGlar 0.68% vs. IGlar 0.88%). Patients with T2DM in the ABET study included 100% insulin-naïve patients, in contrast to ELEMENT-2, in which 39.6% of patients had previously received IGlar.[9] In addition, the assays of these four trials were performed in different laboratories (Wuxi AppTec [Shanghai, China] for ABES/ABET and Millipore [St. Charles, Missouri] for ELEMENT-1/2). The WuXi assay involved the same methodology as the Millipore assay. The pertinent comparison could be an intra-study one, comparing the incidence of anti-insulin antibody across the LY IGlar and IGlar treatment arms.[33,34]

In this analysis, no significant association or differential treatment effect was observed between anti-insulin antibody levels or TEAR status and HbA1c, insulin dose or hypoglycaemia for Chinese patients with T1DM or T2DM receiving LY IGlar or IGlar. In particular, there was no significant interaction between TEAR status (yes or no) and change from baseline HbA1c, insulin dose or overall total hypoglycaemia. This supports similar findings from the ELEMENT-1 and -2 trials and further confirms that immune responses to LY IGlar and IGlar do not affect clinical outcomes.[29] In addition, our results showed no interaction between overall TEAR status and incidence of adverse events, including injection site reactions and serious adverse events. Furthermore, the overall incidence of TEAEs in the present analysis was broadly comparable between patients receiving LY IGlar and IGlar. Among patients with a TEAR, no statistically significant differences were observed in the incidence of adverse events by system organ class between patients receiving LY IGlar or IGlar. There was a statistically significant difference in the incidence of nasopharyngitis among patients with TEAR receiving LY IGlar versus IGlar in the T2DM patient population (0.0% vs. 10.3% [$n = 3$]; $P = 0.031$). However, due to the small patient numbers in this subgroup, this finding should be interpreted cautiously.

The open-label design of the ABES and ABET trials is one potential limitation of this analysis, as it may represent a source of bias. However, LY IGlar and IGlar are provided in differently designed injector pens with different packaging, precluding the masking of interventions. In addition, in the ABES and ABET trials, data were collected over 24 weeks, which is a relatively short treatment duration. Despite this, the findings for patients with T1DM included in the present analysis align well with those from the ELEMENT-1 study after a 52-week treatment duration. This suggests that 24 weeks is a sufficient duration to enable evaluation of immunogenicity.

In conclusion, the immunogenicity profiles of LY IGlar and IGlar are similar in Chinese patients with T1DM and T2DM, with no statistically significant treatment differences in the proportion of patients who developed anti-insulin antibodies, median antibody levels or incidence of TEAR. No association was observed between anti-insulin antibody levels or TEAR and clinical outcomes including HbA1c level, insulin dose and hypoglycaemia. Together with immunogenicity data from the global ELEMENT-1 and -2 trials, these findings further confirm the similar immunogenicity profiles and safety of LY IGlar and IGlar in Chinese patients with T1DM and T2DM.

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SUPPORTING INFORMATION

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