research letter

Efficacy and safety of LY2963016 insulin glargine in patients with type 1 and type 2 diabetes previously treated with insulin glargine

The safety and efficacy of LY2963016 insulin glargine (LY IGlar) and Lantus® insulin glargine (IGlar), products with identical primary amino acid sequences, were assessed in subgroups of patients with type 1 (T1D, n = 452) or type 2 diabetes (T2D, n = 299) reporting prestudy IGlar treatment in 52-week open-label (ELEMENT-1) and 24-week double-blind (ELEMENT-2) studies. At randomization, patients transitioned from their prestudy IGlar to equivalent doses of LY IGlar or IGlar. Primary efficacy (change in glycated haemoglobin from baseline to 24 weeks), other efficacy and select safety outcomes of LY IGlar were compared with those of IGlar. Continuous data were analysed using analysis of covariance, categorical data by Fisher's exact test, and treatment comparisons for hypoglycaemia by Wilcoxon test. No statistically significant treatment differences were identified for efficacy and safety outcomes except for weight change (T1D), overall incidence of detectable insulin antibodies (T2D), and serious adverse events (T2D). These differences were neither consistently observed across both studies nor observed in the total study populations, and their magnitude suggests they were not clinically meaningful. LY IGlar and IGlar show similar efficacy and safety profiles in patients reporting prestudy IGlar treatment.

Keywords: biosimilar insulin, insulin glargine, LY2963016 insulin glargine

Introduction

Lantus® [insulin glargine (rDNA origin); Sanofi-Aventis, Paris, France; IGlar), a protein product manufactured using recombinant DNA technology, was the first long-acting basal insulin analogue approved for the treatment of type 1 (T1D) and type 2 diabetes (T2D) [1,2]. LY2963016 IGlar (LY IGlar), the first biosimilar insulin to receive marketing authorization in the European Union [3] and Japan [4], has an identical primary amino acid sequence to that of IGlar. Biosimilars, which are complex molecules produced through different manufacturing processes, cannot be considered identical to their reference products [5]. Non-clinical, phase I and phase III studies (ELEMENT-1 and ELEMENT-2) demonstrated LY IGlar and IGlar are highly similar [6–9].

In ELEMENT-1, patients with T1D reported prestudy IGlar (prior IGlar) or other basal insulin use [8]. In ELEMENT-2, patients with T2D were either insulin naïve or had prior IGlar use [9]. Results for both full analysis set (FAS) populations [8,9] and prior IGlar and insulin-naïve subgroups (T2D) were previously reported [9]; however, this paper examines whether any treatment differences exist in clinical outcomes between LY

IGlar and IGlar in the prior IGlar subgroups. Such data may be relevant in clinical practice.

Materials and Methods

Methods for both studies, carried out according to ethical principles described in the International Conference on Harmonisation on Good Clinical Practices and Declaration of Helsinki [10], have been reported [8,9]. At randomization, patients received an LY IGlar or IGlar dose that was equivalent to their prestudy IGlar dose. Prefilled pen devices [9] or covered vials and syringes [9] were used to deliver study drug. Both studies used treat-to-target approaches to achieve protocol-specified glycaemic goals [8,9].

In each study, separate analyses compared LY IGlar to IGlar for the prior IGlar subgroup. Prespecified analyses included change from baseline in glycated haemoglobin (HbA1c) at 24 weeks (primary efficacy outcome), change in body weight, hypoglycaemia (total, severe and nocturnal), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), adverse events (AEs) leading to discontinuation, allergic events, injection site reactions and insulin antibodies as a categorical outcome [treatment-emergent antibody response (TEAR)] [11]. *Post hoc* analyses included proportion of patients achieving HbA1c targets, basal insulin dose, prandial insulin dose (ELEMENT-1), percent weight change from baseline (ELEMENT-1), fasting plasma glucose (FPG), prior IGlar insulin antibody levels and documented symptomatic hypoglycaemia.

Correspondence to: R. K. Pollom, Eli Lilly and Company, Lilly Corporate Center, 893 South Delaware Street, Indianapolis, IN 46285, USA.
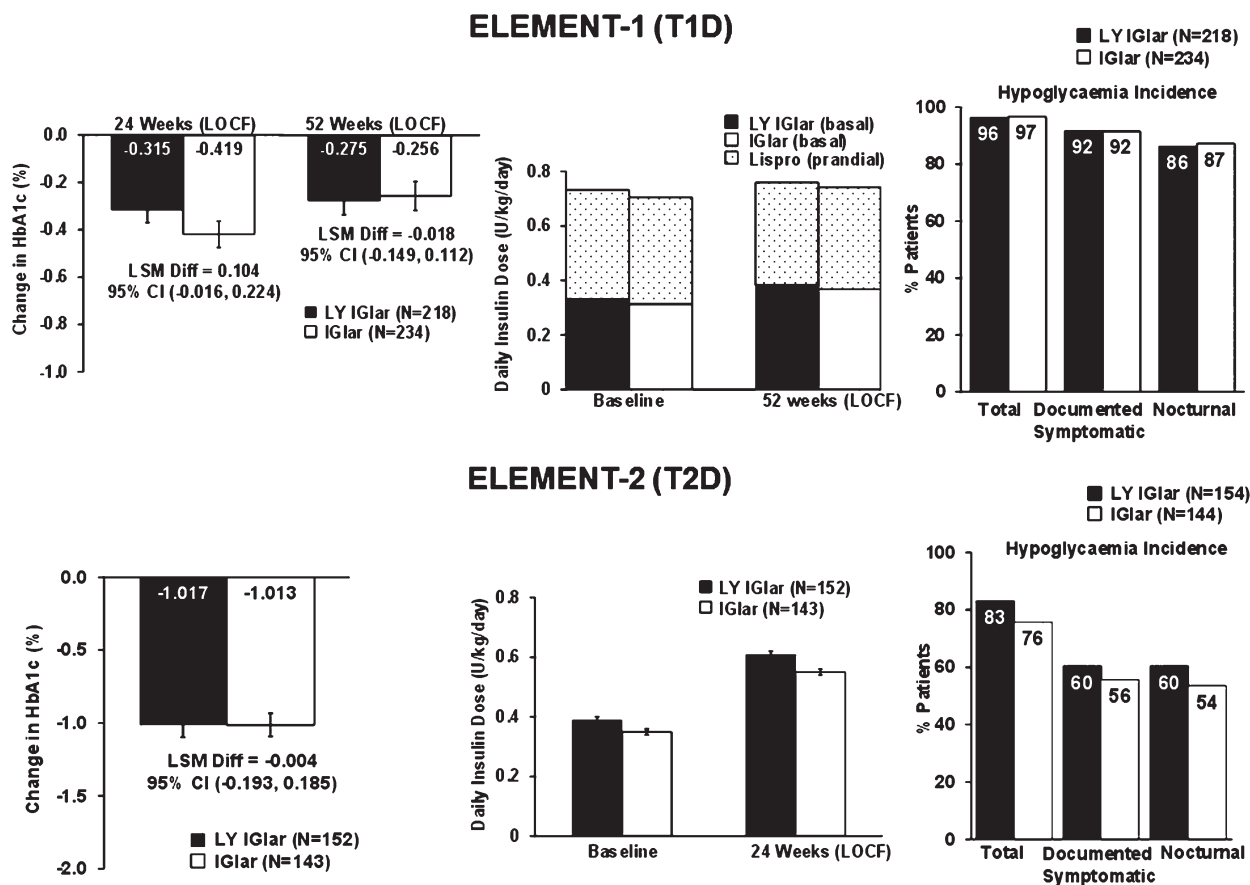E-mail: pollom_robyn_kaye@lilly.com

Figure 1. Efficacy and safety outcomes in the prior IGlar subgroup of patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). All p values >0.05. CI, confidence interval; IGlar, insulin glargine; LOCF, last observation carried forward (endpoint); LSM Diff, least-squares mean difference; LY IGlar, LY2963016 insulin glargine.

Continuous data (HbA1c change, weight change) were analysed using an analysis of covariance model with treatment, country, time of basal insulin injection, sulphonylurea use (ELEMENT-2 only) as fixed effects and baseline value of response variable as a covariate, and the subgroup (prior IGlar at study entry: yes, no), and subgroup-by-treatment interaction. Treatment comparisons were made within the subgroup of patients who reported prestudy treatment with IGlar. Treatment comparisons for insulin antibody levels and hypoglycaemia rates were carried out using the Wilcoxon test. Hypoglycaemia incidence and the proportion of patients achieving HbA1c targets were analysed using the Mantel-Haenszel test. Categorical data (detectable antibodies, TEAR and AEs) were analysed using Fisher's exact test.

The study was registered at ClinicalTrials.gov with trial numbers NCT01421147 and NCT01421459.

Results

Of the 535 patients in the FAS with T1D, 452 (84.5%) reported prestudy IGlar treatment. Of the 756 patients in the FAS with T2D, 299 (39.6%) reported prestudy IGlar treatment. In both studies, baseline characteristics were generally similar between

both groups and consistent with the FAS, except for race in patients with T2D. As expected, patients with T2D who reported prior IGlar had slightly lower baseline HbA1c and FPG than the FAS (Table S1).

In patients with T1D, no statistically significant treatment differences were observed for the primary efficacy measure, change in HbA1c from baseline to the 24-week endpoint [last observation carried forward (LOCF)], and 52-week endpoint (LOCF; Figure 1). No statistically significant treatment differences were observed for the proportions of patients achieving HbA1c targets at 52 weeks (LOCF; Figure S1). Increases in basal and prandial insulin doses (U/kg/day) from baseline to the 52-week endpoint (LOCF) were similar for both treatments (Figure 1). Daily mean blood glucose and FPG at 52 weeks were similar between the two groups (Table S2). A small, statistically significant treatment difference was observed for weight change, where LY IGlar-treated patients gained more weight (Figure S1) with minimal least squares mean percent change from baseline (<2%) [LY IGlar: 1.81 ± 0.42; IGlar: 0.41 ± 0.39; p = 0.035].

In patients with T2D, no significant treatment differences were observed for change in HbA1c from baseline to endpoint (LOCF; Figure 1), the proportion of patients achieving
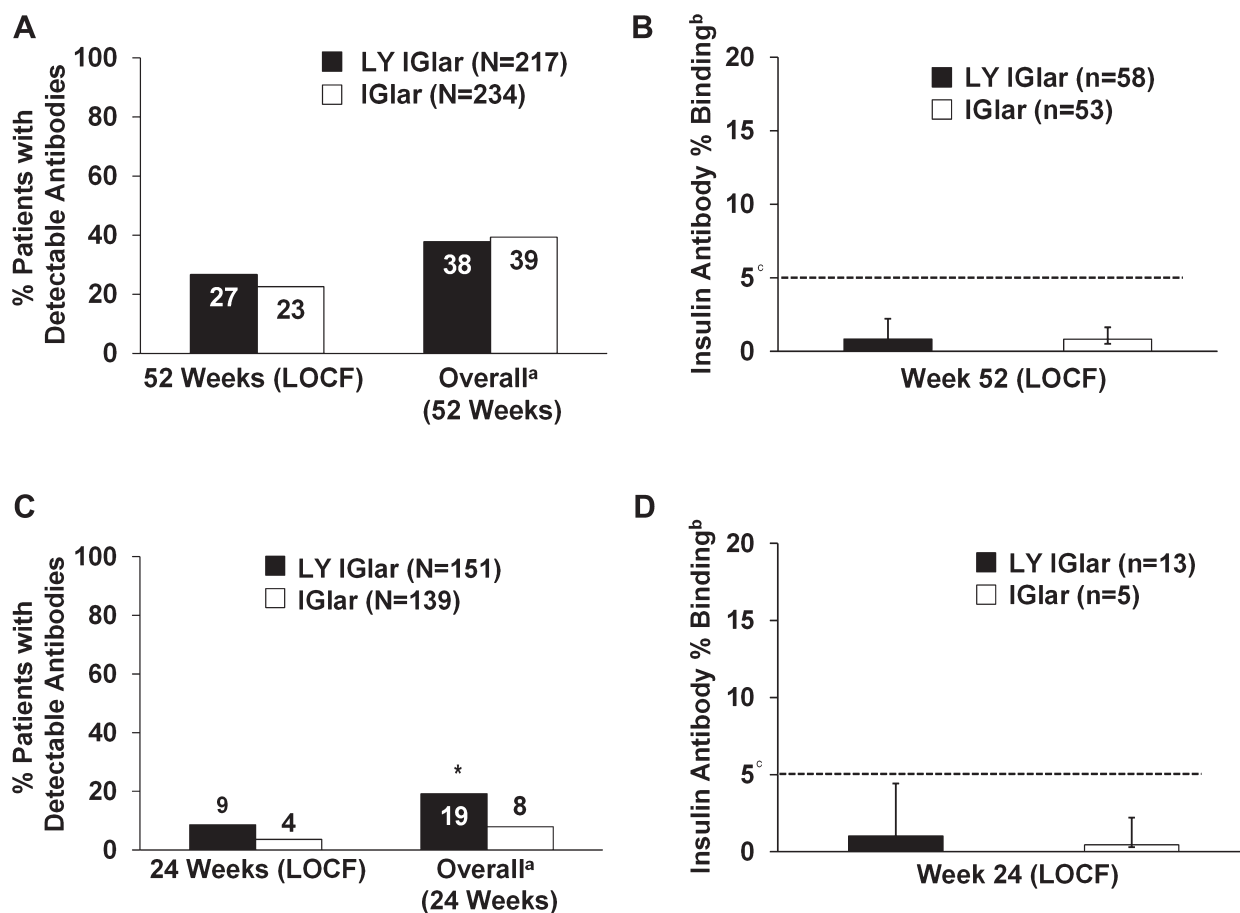
Figure 2. (A) Proportion of patients with detectable antibodies in the prior IGlar subgroup of patients with type 1 diabetes (T1D). All p values >0.05. Only patients with detected or non-detected insulin antibody levels at baseline and post-baseline were included in the analysis. (B) Level of insulin antibodies (percent binding) in patients with detectable antibodies in the prior IGlar subgroup of patients with T1D. [a]Measurements taken at any time/visit postbaseline. [b]Median + interquartile range. [c]Five percent binding level in the screening assay approximately equates to 250 ng/ml (250–500 ng/ml US Food and Drug Administration (FDA)-recommended screening assay sensitivity correlated with clinical events) [12]. Insulin antibody values depicted in the graph are from determinations following screening [11]. All p values >0.05. (C) Proportion of patients with detectable antibodies in the prior IGlar subgroup of patients with type 2 diabetes (T2D). *p = 0.01; all other p values >0.05. Only patients with detected or non-detected insulin antibody levels at baseline and post-baseline were included in the analysis. (D) Level of insulin antibodies (percent binding) in patients with detectable antibodies in the prior IGlar subgroup of patients with T2D. [a]Measurements taken at any time/visit post-baseline. [b]Median + interquartile range. [c]Five percent binding level in the screening assay approximately equates to 250 ng/ml (250–500 ng/ml FDA-recommended screening assay sensitivity correlated with clinical events) [12]. Insulin antibody values depicted in the graph are from determinations following screening [11]. All p values >0.05. IGlar, insulin glargine; LOCF, last observation carried forward (endpoint); LY IGlar, LY2963016 insulin glargine.

glycaemic targets (Figure S1), mean FPG and daily mean blood glucose (Table S2), basal insulin dose (Figure 1) and weight change (Figure S1).

In patients with T1D, the overall incidence of total, documented symptomatic, nocturnal (Figure 1) and severe hypoglycaemia (LY IGlar: 5%; IGlar: 4%, p = 0.816) was similar for both groups throughout the 52-week study. Likewise, overall 1-year adjusted hypoglycaemia rates were similar (Figure S1). Severe hypoglycaemia rates were not statistically compared because of the low number of events in each treatment arm.

In patients with T2D, the incidence of total, documented symptomatic and nocturnal hypoglycaemia was similar for both groups during the 24-week study (Figure 1). No patients reported severe hypoglycaemia. The 1-year adjusted hypoglycaemia rates were similar in the two groups (Figure S1).

No significant treatment differences were observed in the proportion of patients with T1D with detectable antibodies at the 52-week endpoint and overall (Figure 2A). Median insulin antibody levels were also similar and low (<5%) for both groups at 52 weeks (LOCF; Figure 2B) [12]. Likewise, the incidence of TEAR was similar at the endpoint [LOCF; LY IGlar: 15 patients (7%), IGlar: nine patients (4%); p = 0.148] and overall [LY IGlar: 21 patients (10%), IGlar: 21 patients (9%); p = 0.798].

The overall proportion of detectable antibodies in LY IGlar-treated patients with T2D was statistically significantly higher than IGlar-treated patients (Figure 2C), which may be the result of more patients with detectable antibodies being randomly assigned to the LY IGlar group at baseline [11]; however, the incidence of patients with detectable

antibodies was similar at the 24-week endpoint [11]. Median insulin antibody levels were low (<5% binding) and similar between the two groups at the 24-week-endpoint (LOCF; Figure 2D) [12]. Endpoint and overall incidence of TEAR were similar [11].

The incidence of AEs and SAEs, injection site reactions and allergic events was similar for both groups in both studies (Table S3); however, significantly fewer LY IGlar-treated patients with T2D experienced ≥1 SAE than IGlar-treated patients. The incidence of SAEs in both treatment groups was <1% for all preferred terms with no significant treatment differences.

Discussion

The results of the present study were intended to address questions about clinical outcomes when LY IGlar is compared with IGlar in the prior IGlar subgroup of patients with T1D or T2D. No treatment differences were observed for the primary and other clinical outcomes, except as noted.

A significant treatment difference in weight change was noted for patients with T1D. The weight gain for LY IGlar was somewhat higher in the prior IGlar subgroup than in the FAS [9]. This trend is reversed for IGlar in the FAS [8]. The weight gain with LY IGlar falls within reported weight changes with insulin glargine [13,14]. Moreover, a widespread weight change was observed in both groups (LY IGlar: median = 0.85, range −7.10 to 15.20; IGlar: median = 0.10, range −14.20 to 18.40). This treatment difference was not observed in either the FAS [8, 9] or in the prior IGlar subgroup of patients with T2D [9], suggesting this observed difference is probably a chance finding.

The statistically significant difference in overall antibody incidence of LY IGlar-treated patients with T2D could be explained by an imbalance in baseline antibody levels. The difference was not observed at the 24-week endpoint (LOCF) [11]. The incidence of detectable antibodies was notably lower at endpoint than for overall, which included patients who were positive for antibodies at any time during the study but may have had subsequent non-detectable antibody levels. Furthermore, both groups had similar median insulin antibody levels and similar proportions of patients with TEAR. No differences were observed in the prior IGlar subgroup of patients with T1D or in the FAS for both studies [8, 9].

Finally, data from both FAS populations of patients show no evidence that these antibodies had any impact on efficacy and safety outcomes [11]. Although significantly fewer LY IGlar-treated patients with T2D experienced ≥1 SAE, there were no significant differences in preferred terms (Table S4).

One limitation of the present results is that neither study was designed to prospectively compare LY IGlar and IGlar in patients with diabetes reporting prestudy IGlar treatment and the results should not be considered sufficient to support interchangeability. The decision to transition patients from one type of insulin to another should be made by the prescribing healthcare professional and according to existing product labels [1,6] and country-specific guidelines [15].

In conclusion, our results show that patients reporting prestudy IGlar treatment who were randomized to LY IGlar have similar efficacy and safety outcomes to those of patients receiving IGlar. The majority of our findings were consistent with those of the FAS of patients with T1D or T2D [8,9]. Data from these subgroup analyses suggest LY IGlar is a well tolerated and effective treatment option when prescribed for patients with T1D and T2D who have had prior treatment with IGlar.

I. Hadjiyianni[1], D. Dahl[2], L. B. Lacaya[3], R. K. Pollom[3], C. L. Chang[3,4] & L. L. Ilag[3]

[1]*Lilly Deutschland GmbH, Bad Homburg, Germany*
[2]*Gemeinschaftspraxis für Innere Medizin und Diabetologie, Hamburg, Germany*
[3]*Eli Lilly and Company, Indianapolis, IN, USA*
[4]*Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi City, Taiwan*

Conflict of Interest

I. H., L. B. L., R. K. P., C. L. C. and L. L. I., are employees of and hold stock in Eli Lilly and Company. D. D. has no conflicts of interest to disclose.

I. H. participated in the interpretation and discussion of the research, and in writing the manuscript. D. D. contributed to the interpretation and discussion of the research, in conducting the study and reviewed and edited the manuscript. L. B. L. and L. L. I. participated in the study design, in conducting the study, in the data analysis, in the interpretation and discussion of the research and in writing the manuscript. R. K. P. participated in conducting the study, in the data analysis, in the interpretation and discussion of the research and in writing the manuscript. C. L. C. participated in the interpretation and discussion of the research and in writing the manuscript. All authors approved the version to be published. R. K. P is the guarantor of this work and, as such, takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. Eileen Girten (non-author) prepared the draft manuscript and provided editorial support.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Efficacy and safety outcomes in the prior IGlar subgroup of patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). *$p = 0.016$ for LY IGlar vs IGlar; all other p-values >0.05. Abbreviations: IGlar, insulin glargine; LSM, least squares mean; LY IGlar, LY2963016 insulin glargine; SD, standard deviation; SE, standard error.

Table S1. Patient demographics and baseline characteristics for the total study population and prior IGlar subgroup in patients with type 1 or type 2 diabetes.

Table S2. Fasting plasma glucose and daily mean glucose in the prior IGlar subgroup of patients with type 1 or type 2 diabetes.

Table S3. Adverse events summary for prior IGlar subgroup of patients with type 1 or type 2 diabetes.

Table S4. Summary of serious adverse events for prior IGlar patients with type 2 diabetes.

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