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ORIGINAL ARTICLE

Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study)

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Aims: To compare the efficacy and safety of LY2963016 insulin glargine (LY IGlar) and the reference product (Lantus®) insulin glargine (IGlar) in combination with oral antihyperglycaemic medications in patients with type 2 diabetes (T2D).

Methods: This phase III, randomized, double-blind, 24-week study enrolled patients with T2D who were insulin-naïve [glycated haemoglobin (HbA1c) ≥7 and ≤11.0%] or previously on IGlar (HbA1c ≤11%) and treated with ≥2 oral antihyperglycaemic medications. Patients were randomized to receive once-daily LY IGlar (n = 376) or IGlar (n = 380) for 24 weeks. The primary efficacy outcome was to test the non-inferiority (0.4% and then 0.3% margin) of LY IGlar to IGlar, as measured by change in HbA1c from baseline to 24 weeks.

Results: Both treatment groups had similar and significant ($p < 0.001$) within-group decreases in mean HbA1c values from baseline. LY IGlar met non-inferiority criteria compared with IGlar for change in HbA1c from baseline [−1.29 vs −1.34%; respectively, least-squares mean difference 0.052% (95% confidence interval −0.070 to 0.175); $p > 0.05$]. There were no treatment differences ($p > 0.05$) in fasting plasma glucose, proportion of patients reaching HbA1c <7% or insulin dose at 24 weeks. Adverse events, allergic reactions, weight change, hypoglycaemia and insulin antibodies were similar between treatment groups. Similar findings were observed in patients who were insulin-naïve or previously treated with IGlar at baseline.

Conclusions: Both LY IGlar and IGlar, when used in combination with oral antihyperglycaemic medications, provided effective and similar glucose control with similar safety profiles in patients with T2D.

Keywords: LY2963016, insulin glargine, type 2 diabetes, insulin-naive

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Introduction

Type 2 diabetes (T2D) is characterized by progressive deterioration and loss of β-cell function. Once oral therapy has become inadequate, the addition of basal insulin to an oral antihyperglycaemic medication regimen is often advised [1,2]. In patients with T2D, insulin glargine [IGlar; Lantus®, Sanofi-Aventis, Paris, France (rDNA origin)] has been shown to provide similar glycaemic control to that of NPH insulin, but with a lower risk of hypoglycaemia [3–7].

LY2963016 insulin glargine (LY IGlar) is the first biosimilar insulin approved for marketing authorization in the European Union (September 2014) [8]. This long-acting human insulin analogue has an identical amino acid sequence and the same pharmaceutical form and strength, i.e. concentration of the active ingredient, as IGlar [9]. Biologicals that are approved based on similarity to an already marketed protein product (reference product) are sometimes referred to as 'biosimilars' (e.g. in the European Union and Japan) or using other terminology (e.g. 'subsequent entry biologics' in Canada) based on the applicable regulatory designation. In the USA, IGlar, the reference product for LY IGlar, was approved through the new drug application pathway [10] which necessitated the filing of LY IGlar through the 505(b)(2) regulatory pathway [11], and not the 351(k) biosimilar pathway [12]; therefore, LY IGlar is not considered to be a biosimilar in the USA. The development of a similar biological product (biosimilar) relies, in part, on the scientific knowledge gained from the reference product, provided that the active substance of the biosimilar has been demonstrated to be similar, in physicochemical and biological terms, to the active substance of the reference product [13]. Specific guidance from regulatory agencies outlines the data requirements for establishing similarity with a marketed biological

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product [14–17]. The scientific principles in demonstrating the similarity of LY IGlar to IGlar are consistent with this guidance and with the requirements for demonstrating similarity between two biological products.

As part of the LY IGlar development programme that was designed to fulfill regulatory requirements, preclinical, phase I and phase III studies were performed. LY IGlar and IGlar were shown to have similar pharmacokinetic and pharmacodynamic properties [18–21]. In patients with type 1 diabetes (T1D), LY IGlar compared with IGlar, used in combination with insulin lispro, provided equivalent efficacy and a similar safety profile with no clinically meaningful differences [22].

The present manuscript reports on the phase III clinical trial that compared the efficacy and safety of LY IGlar and IGlar in combination with oral antihyperglycaemic medications in patients with T2D previously treated with insulin glargine or who were insulin-naïve.

Methods

Study Design and Patients

This phase III, randomized, multinational, multicentre, two-arm, active-controlled, double-blind, parallel study had a 24-week treatment period with a 4-week post-treatment follow-up in patients with T2D (Figure S1). The primary objective of the study was to show the non-inferiority of LY IGlar once daily to IGlar once daily, as measured by change in glycated haemoglobin (HbA1c), from baseline to 24 weeks, when used in combination with oral antihyperglycaemic medications. The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki [23]. All patients provided written informed consent. The study was registered at Clinical.Trials.gov under the number NCT01421459. The ELEMENT 2 study investigators are listed in File S1.

Eligible study participants had T2D based on World Health Organisation diagnostic criteria [24], were aged ≥18 years, had been receiving ≥2 oral antihyperglycaemic medications at stable doses for 12 weeks before screening (with or without IGlar), had HbA1c levels ≥7.0 and ≤11.0% if insulin-naïve or ≤11.0% if previously on IGlar, and had a body mass index ≤45 kg/m^2. Exclusion criteria included treatment with pramlintide (Symlin®) or any other insulin except IGlar within the previous 30 days, treatment with a biosimilar insulin glargine within the previous 90 days, history of receiving basal-bolus therapy or, in the investigator's opinion, requirment for mealtime insulin to achieve target control, total daily insulin dose ≥1.5 U/kg, and more than one episode of severe hypoglycaemia within the past 6 months.

Treatment assignment was stratified on the basis of country, HbA1c value (<8.5% vs ≥8.5%), sulphonylurea use (yes or no), and time of basal insulin injection (daytime or evening/bedtime). Clinic visits occurred at screening, randomization (week 0) and weeks 2, 4, 8, 12, 16, 20 and 24. Patients randomized to treatment (LY IGlar or IGlar) were provided with covered insulin vials (for blinding purposes) and syringes during the study. The starting dose for all insulin-naïve patients was 10 U/day. Patients entering the study on IGlar were randomized to either LY IGlar or IGlar at a dose equivalent to their prestudy IGlar dose. A patient-driven titration schedule of adding 1 unit daily until fasting plasma glucose (FPG) levels reached ≤5.6 mmol/l (100 mg/dl) was followed [25]; investigators had the discretion to decrease insulin dose for patients experiencing hypoglycaemia on their active dose while attempting to maintain the target FPG. It was anticipated that most of the titration would be largely completed during the titration period (weeks 0–12), with any further adjustments made after week 12 for safety concerns such as hypoglycaemia or unacceptable hyperglycaemia as determined by the investigator.

Outcomes

The HbA1c analyses were conducted by a central laboratory (Covance, Indianapolis, IN, USA) using the Variant II and Variant II Turbo HbA1c testing systems (Bio-Rad Laboratories, Hercules, CA, USA). Seven-point self-monitored blood glucose (SMBG) profiles (pre-meal for each meal, post-meal for breakfast and lunch, bedtime and 03:00 hours) were collected three times in the 2 weeks before each clinic visit and measured using study-provided glucometers (Accu-Chek Aviva\Performa; Roche, Indianapolis, IN, USA). Intrapatient FPG variability was calculated based on the standard deviation of the morning pre-meal blood glucose value. Adverse events (AEs), defined as events that were reported as new or worsening in severity after randomization, were documented at every visit. Clinical chemistry and haematology panels were collected at baseline and week 24. Insulin antibodies were quantified as percent binding using a classic radioimmunoassay format. The anti-LY IGlar antibody assay has cross-reactivity to IGlar and human insulin; hence antibodies to LY IGlar and IGlar were measured using the same assay. During validation, an assay threshold of 0.26% bound/total was determined to indicate binding to LY IGlar. Sensitivity of the method was determined to be 25 ng/ml using a polyclonal affinity purified anti-insulin antibody assay.

Hypoglycaemia was defined as blood glucose ≤3.9 mmol/l (≤70 mg/dl) or a sign or symptom associated with hypoglycaemia. Nocturnal hypoglycaemia was defined as any hypoglycaemic event that occurred between bedtime and waking. Severe hypoglycaemia was defined as a hypoglycaemic event requiring the assistance of another person to actively administer treatment or other resuscitative actions. All severe hypoglycaemia episodes were reported as serious AEs (SAEs).

Other safety assessments included the special topic assessment of allergic reactions and injection site AEs. Injection site AEs were evaluated for pain, pruritus and rash associated with the injection, as well as the characteristics of the injection site (abscess, nodule, lipoatrophy, lipohypertrophy or induration). Allergic or immunological conditions were assessed by determining the frequency and severity of AEs from a prespecified list of AE terms.

Statistical Analyses

The non-inferiority design is in accordance with regulatory requirements [26–28]. Based on the primary objective, to show

non-inferiority of LY IGlar to IGlar at the 0.4% non-inferiority margin (NIM), and 0.3% NIM if the 0.4% NIM was met, 284 (568 total) completers per arm were needed at 24 weeks. This calculation assumed no treatment difference in HbA1c between LY IGlar and IGlar, a common standard deviation of 1.1% for change from baseline in HbA1c, 0.05 two-sided significance level and 90% power for a 0.3% NIM, and >99% power for a 0.4% NIM. Assuming a 15% dropout rate at 24 weeks, the required number of randomized patients was 334 per arm (668 total).

Analyses were conducted using SAS version 9.1.3 (SAS Drug Development, Cary, NC, USA) and were based on all patients who were randomized and took ≥1 dose of study drug, defined as the full analysis set, a slightly modified intent-to-treat population. If the measurement for a visit was missing, the previous non-missing measurement was analysed using the last-observation-carried-forward (LOCF) methodology. All tests of treatment effects were conducted at a two-sided α level of 0.05 and confidence intervals (CIs) were calculated as two-sided 95% CIs. All tests of interactions between treatment groups and other factors were conducted at a two-sided α level of 0.05. No adjustments for multiplicity were performed.

The primary efficacy measure was the change in HbA1c from baseline to the 24-week endpoint, defined as the value at 24 weeks or LOCF. The primary analysis model was an analysis of covariance (ANCOVA) for the change from baseline to endpoint with pooled country, sulphonylurea use (yes or no), time of basal insulin injection (daytime or evening/bedtime), and treatment as fixed effects and baseline HbA1c as a covariate. The primary treatment comparison was to compare LY IGlar with IGlar at the NIM of 0.4%. If the upper limit of the 95% CI on the change in HbA1c from baseline to the 24-week endpoint for LY IGlar versus IGlar was <0.4%, then LY IGlar was declared non-inferior to IGlar. If the 0.4% NIM was met, then the upper limit of the 95% CI was compared with the 0.3% NIM. This gate-keeping procedure controlled the family-wise type 1 error rate at a one-sided 0.025 level.

A key secondary treatment comparison was to compare IGlar with LY IGlar at the NIM of −0.4%; therefore, if LY IGlar was declared non-inferior to IGlar in the primary treatment comparison as described above, and IGlar was also declared non-inferior to LY IGlar in the secondary treatment comparison, then LY IGlar was considered to have equivalent efficacy to IGlar.

The analysis of the continuous secondary efficacy outcomes used the ANCOVA model which was used for the primary efficacy outcome. The proportion of patients achieving HbA1c target values (HbA1c <7.0 and ≤6.5%) during the study was analysed using Fisher's exact test. Hypoglycaemia rate, expressed as events per patient per year, was analysed using a negative binomial model with terms for treatment and other stratification variables.

A subgroup analysis of the HbA1c levels examined the consistency of the treatment effect for the subgroup defined by entry basal insulin treatment. The change in HbA1c from baseline to 24-week endpoint (LOCF) was analysed using ANCOVA with treatment, country, sulphonylurea use (yes or no), time of basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as a covariate, and the subgroup [i.e. entry basal insulin treatment (IGlar, none)], and subgroup-by-treatment interaction. Similar subgroup analyses were performed for other efficacy outcomes.

Table 1. Patient demographics and baseline characteristics.

	LY IGlar N = 376*	IGlar N = 380*
Age, years	59 ± 10	59 ± 10
<65 years, n (%)	264 (70)	278 (73)
Male, n (%)	179 (48)	199 (52)
Race, n (%)		
American Indian or Alaska Native	17 (5)	21 (6)
Asian	29 (8)	35 (9)
Black	26 (7)	32 (8)
Mixed race	2 (1)	1 (<1)
White	302 (80)	291 (77)
Body weight, kg	90 ± 20	90 ± 19
Body mass index, kg/m^2	32 ± 6	32 ± 5
HbA1c		
%	8.34 ± 1.09	8.31 ± 1.06
mmol/mol	68 ± 12	67 ± 12
Entry HbA1c, n (%)		
<8.5% (<69 mmol/mol)	209 (56)	210 (55)
<7.0% (<53 mmol/mol)	19 (5)	25 (7)
FPG†		
mg/dl	159 ± 45	160 ± 44
mmol/l	8.82 ± 2.50	8.86 ± 2.42
Duration of diabetes, years	12 ± 7	11 ± 7
Basal insulin, n (%)		
IGlar	155 (41)	144 (38)
None	221 (59)	236 (62)
Time of basal insulin injection, n (%)		
Daytime	187 (50)	188 (50)
Evening/bedtime	189 (50)	192 (51)
Sulphonylurea use, n (%)	315 (84)	315 (83)

Data are mean ± standard deviaion, unless otherwise indicated. p > 0.05 for all treatment comparisons. FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IGlar, insulin glargine; LY IGlar, LY2963016 insulin glargine; SMBG, self-monitored blood glucose.
*Full analysis set, N numbers reflect maximum sample size.
†By SMBG.

Results

Patients

Of the 756 patients included in the full analysis set population, 88% completed the 24-week treatment period. Patient decision (e.g. busy work schedule, relocation, family problems, fear of needles) was the most common reason for study discontinuation in both groups (Figure S2). The demographic characteristics of both treatment groups were well balanced (Table 1). In all, 621 patients (82.1%) were receiving two oral antihyperglycaemic medications before randomization, with significantly fewer patients in the LY IGlar group receiving two oral antihyperglycaemic medications compared with the IGlar group [LY IGlar: 298 patients (79.3%); IGlar: 323 patients (85.0%); p = 0.046]. The most common combinations of two oral antihyperglycaemic medications were metformin and sulphonylurea

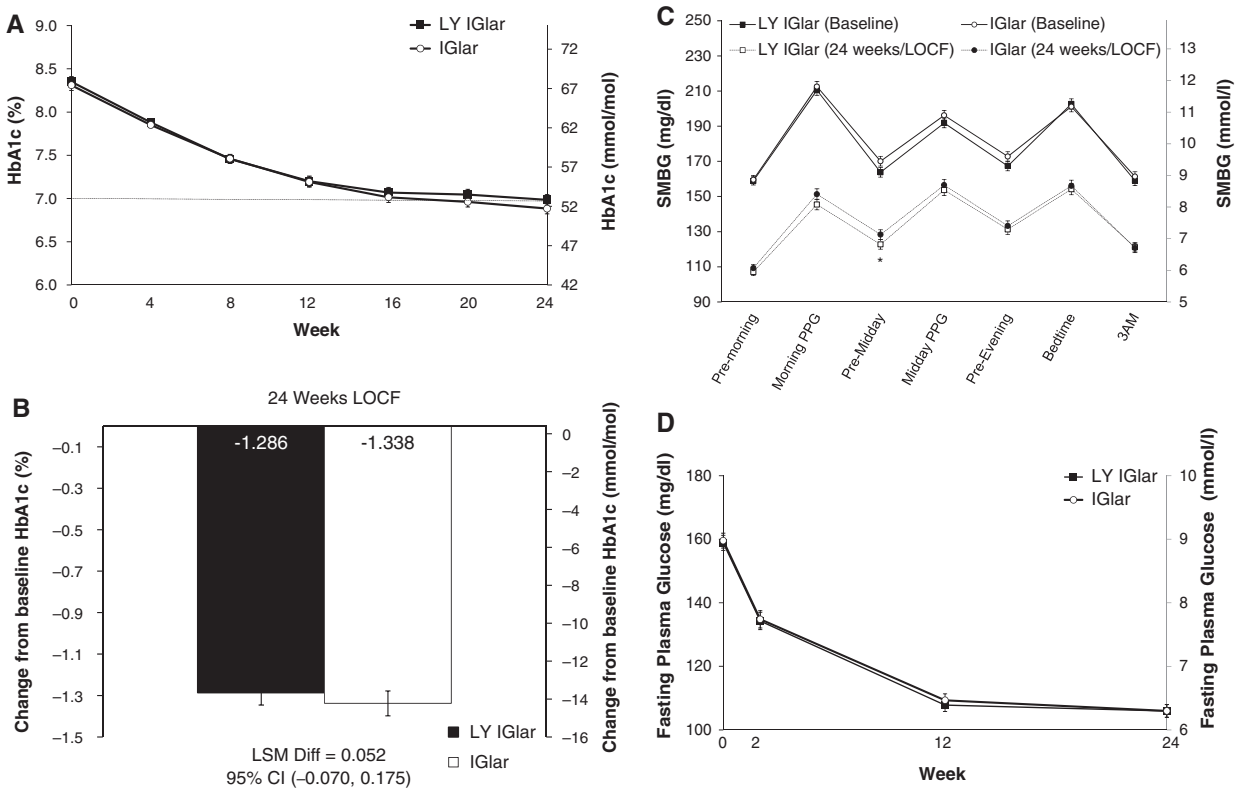

Figure 1. (A) Change in absolute glycated haemoglobin (HbA1c) over 24 weeks. (B) Change from baseline HbA1c at 24 weeks LOCF. (C) Self-monitored blood glucose (SMBG) at baseline and 24 weeks LOCF. (D) Fasting plasma glucose over 24 weeks. Data are least squares means ± standard error. Open circles: insulin glargine (IGlar); closed squares: LY2963016 insulin glargine (LY IGlar). *p = 0.04 for treatment difference.

(62.4% of total patients), and dipeptidyl peptidase-4 inhibitors and metformin (10.1% of total patients). Analyses of baseline and demographic characteristics in the subgroups of patients previously on IGlar and insulin-naïve at study entry, showed that all variables were balanced with the exception of race, where there was a greater proportion of white people in the LY IGlar group than in the patients previously treated with IGlar subgroup of the IGlar group (Table S1).

Efficacy

Both treatment groups had within-group significant ($p < 0.001$) decreases in least squares (LS) mean HbA1c values from baseline, which began at visit 4 (week 6) and continued through to the 24-week endpoint (LOCF; Figure 1A). The primary efficacy outcome was met with the demonstration of non-inferiority of LY IGlar to IGlar on change in HbA1c from baseline to the 24-week endpoint at both the 0.4 and 0.3% NIMs. Non-inferiority of IGlar to LY IGlar at the same NIMs was also demonstrated (Figure 1B, Table 2). Collectively, the non-inferiority results indicate that LY IGlar and IGlar have equivalent efficacy. After adjustment for baseline differences for oral antihyperglycaemic medications and race, there were still no treatment differences for change in HbA1c at endpoint. At the 24-week endpoint (LOCF), the proportions of patients achieving the target HbA1c goals of <7.0 and ≤6.5% were not significantly different between treatment groups (Table 2).

Figure 1C is a graphical summary of seven-point SMBG mean values for each time point at baseline and 24 weeks LOCF for both treatment groups. At endpoint (LOCF), the LS mean blood glucose value was lower in the LY IGlar group compared with the IGlar group at the morning 2-h postprandial time point (LY IGlar, 8.07 mmol/L; IGlar, 8.40 mmmol/L; LS mean difference −0.33 mmol/L; $p = 0.050$), and significantly lower at the mid-day pre-meal time point (LY IGlar, 6.81 mmol/L; IGlar, 7.12 mmol/L; LS mean difference −0.31 mmol/L; $p = 0.040$). At all time points, improvements between baseline and endpoint (LOCF) were observed for both treatment groups. No statistically significant treatment differences were observed for any other time point at any visit or endpoint (LOCF). Both treatment groups had decreases in FPG from baseline to endpoint, and there were no statistically significant differences between treatment groups at any visit (Figure 1D). Additionally, there were no statistically significant differences between treatment groups in FPG variability at 24 weeks endpoint [LOCF; LS mean difference (standard error) 0.02 (0.06) mmol/L; $p = 0.788$].

Mean daily insulin dose was similar in both treatment groups at 24 weeks LOCF (Table 2). Patients in both treatment groups experienced weight gain of ~2 kg, with no statistically significant differences between treatment groups for change in body weight from baseline to endpoint (LOCF; Table 2).

A subgroup analysis for select efficacy endpoints by entry basal insulin treatment (IGlar, none) found no significant treatment-by-entry basal insulin treatment interaction for

Table 2. Clinical assessments at study endpoint.

	LY IGlar N = 376*	IGlar N = 380*
HbA1c (%)		
Endpoint	7.04 ± 0.06	6.99 ± 0.06
Change from baseline	−1.29 ± 0.06	−1.34 ± 0.06
LS mean difference (95% CI)	0.052 (−0.070, 0.175)	
HbA1c, mmol/mol		
Endpoint	53 ± 1	53 ± 1
Change from baseline	−14 ± 1	−15 ± 1
LS mean difference (95% CI)	0.6 (−0.8, 1.9)	
Target HbA1c, n (%)		
<7.0% (<53 mmol/mol)	180 (49)	197 (53)
≤6.5% (≤48 mmol/mol)	99 (27)	114 (30)
FPG†(change from baseline)		
mg/dl	−48 ± 3	−46 ± 3
mmol/l	−2.64 ± 0.17	−2.58 ± 0.17
Insulin dose, U/kg/day	0.50 ± 0.03	0.48 ± 0.03
Hypoglycaemia rate overall‡ mean ± s.d.		
Total	21.3 ± 24.4	22.3 ± 28.2
Nocturnal§	7.6 ± 11.8	8.1 ± 14.6
Severe	0.04 ± 0.66	0.01 ± 0.16
Weight change, kg	1.8 ± 0.3	2.0 ± 0.3
Patients with detectable antibodies overall¶ n (%)	56 (15)	40 (11)
% insulin antibody binding at 24 weeks (median)	1.07	0.65

Data are LS mean ± standard error, unless otherwise indicated and from LOCF, unless otherwise indicated. $p > 0.05$ for all treatment comparisons. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IGlar, insulin glargine; LOCF, last observation carried forward (endpoint); LS, least squares; LY IGlar, LY2963016 insulin glargine; s.d., standard deviation; SMBG, self-monitored blood glucose.

*Full analysis set, N numbers reflect maximum sample size.

†By SMBG.

‡Events/patient/1 year. The overall rate at 24 weeks accounts for all events reported during the 24-week treatment period.

§Including events with blood glucose ≤70 mg/dl.

¶Measured for the overall 24-week treatment period and not at LOCF.

change in HbA1c from baseline to endpoint (LOCF), for change in FPG from baseline to endpoint (LOCF), for weight change, or for insulin dose at endpoint, indicating no significant differential treatment effect on these efficacy endpoints for patients entering the study on IGlar and for insulin-naïve patients (Table 3).

Safety

There were no significant differences between treatment groups for the rate of each category of hypoglycaemia (total, nocturnal and severe), adjusted for 1 year, at 24 weeks (Table 2). The rate of documented symptomatic hypoglycaemia blood glucose ≤70 mg/dl (≤3.9 mmol/l) at 24 weeks was also similar ($p = 0.935$) between treatment groups. Similarly, there were no significant treatment differences in the incidence of total hypoglycaemia for 24 weeks (LY IGlar 79%; IGlar 78%; $p = 0.594$), in the incidence of nocturnal hypoglycaemia for 24 weeks (LY IGlar 57%; IGlar 54%; $p = 0.462$), and in the incidence of severe hypoglycaemia for 24 weeks (LY IGlar <1%; IGlar <1%). A subgroup analysis for hypoglycaemia by entry basal insulin treatment (IGlar, none) showed no significant treatment-by-entry basal insulin treatment interaction on the rate of any category of hypoglycaemia for patients entering the study on IGlar, or insulin-naïve patients (Table 3).

Table 4 provides an overview of AEs reported during the 24-week study for the full analysis set population. The incidences of AEs and SAEs reported for LY IGlar were similar to those for IGlar. The most frequently reported AEs were nasopharyngitis (5.7%), upper respiratory tract infection (4.5%) and diarrhoea (3.0%). There were two deaths during the study, one as a result of myocardial infarction (IGlar) and one as a result of lung adenocarcinoma (LY IGlar); neither was considered by the investigator to be related to the study drug. The incidence of allergic reactions was similar among treatment groups; most events were mild or moderate in severity and none led to discontinuation (Table 4). The incidence of injection site AEs was similar between treatment groups; most patients reporting injection site AEs reported having mild or moderate pain associated with the injection (Table 4). A total of 96 patients (13.2%) had detectable antibodies to insulin, and there were no statistically significant treatment differences (Table 2). In addition, there was no statistically significant difference between treatment groups in median insulin antibody-binding values observed at 24-weeks (LOCF; Table 2). No clinically meaningful baseline to endpoint changes in any laboratory values were identified within or between groups (data not shown).

Discussion

Because of the complex structure of biologics and the distinct manufacturing processes involved in their production, LY IGlar must be shown to have similar physicochemical and biological characteristics and a similar safety and efficacy profile to those of the reference product, IGlar, in order to gain regulatory approval [13]. Minor differences between the biosimilar and reference drug in clinically inactive components may occur and there should be no clinically meaningful differences in terms of safety, purity and potency [29]. In the present phase III clinical trial, we evaluated the efficacy and safety of LY IGlar versus IGlar in patients with T2D.

Non-inferiority of LY IGlar to IGlar, as measured by change in HbA1c from baseline to the week 24 endpoint, when used in combination with oral antihyperglycaemic medications, was shown at the NIM of 0.3%, meeting regulatory requirements [26–28]. Both treatment groups had statistically significant within-group decreases in HbA1c from baseline to the 24-week endpoint. LY IGlar and IGlar resulted in similar lowering of blood glucose levels by SMBG from baseline to week 24 of the study, with similar changes in insulin dose and weight between treatment groups. The safety profiles for LY IGlar and IGlar were similar and LY IGlar was well tolerated. Similar safety and efficacy results were seen in subgroup analyses of patients entering the study on previous IGlar versus insulin-naïve patients.

The present study did not show any significant differences in safety measures between the treatment groups. The incidence and rate of hypoglycaemia for any category of hypoglycaemia

Table 3. Clinical assessments at study endpoint for patients who entered the study on insulin glargine and insulin-naïve patients.

	Insulin-naïve		Prior IGlar	
	LY IGlar N = 220*	IGlar N = 235*	LY IGlar N = 155*	IGlar N = 144*
HbA1c, %				
Endpoint HbA1c	6.86 ± 0.07	6.79 ± 0.07	7.31 ± 0.08	7.32 ± 0.08
Change from baseline	−1.48 ± 0.07	−1.54 ± 0.07	−1.02 ± 0.08	−1.01 ± 0.08
LS mean difference (95% CI)	0.061 (−0.091, 0.214)		−0.004 (−0.193, 0.185)	
HbA1c, mmol/mol				
Endpoint HbA1c	51 ± 1	51 ± 1	56 ± 1	56 ± 1
Change from baseline	−16 ± 1	−17 ± 1	−11 ± 1	−11 ± 1
LS mean difference (95% CI)	0.7 (−1.0, 2.3)		−0.1 (−2.1, 2.0)	
Target HbA1c, n (%)				
<7% (<53 mmol/mol)	117 (54)	139 (60)	63 (41)	58 (41)
≤6.5% (≤48 mmol/mol)	65 (30)	86 (37)	34 (22)	28 (20)
FPG†(change from baseline)				
mg/dl	−57 ± 3	−56 ± 3	−34 ± 4	−30 ± 4
mmol/l	−3.16 ± 0.19	−3.09 ± 0.19	−1.86 ± 0.22	−1.68 ± 0.22
Insulin dose, U/kg/day	0.42 ± 0.03	0.44 ± 0.03	0.60 ± 0.03	0.53 ± 0.03
Hypoglycaemia rate overall‡, mean ± s.d.				
Total	21.6 ± 25.6	22.9 ± 27.4	20.8 ± 22.7	21.5 ± 29.6
Nocturnal§	6.7 ± 10.7	7.6 ± 12.5	8.5 ± 13.1	8.8 ± 17.5
Severe	(n = 2)	(n = 2)	—	—
Weight change, kg	2.0 ± 0.3	2.2 ± 0.3	1.4 ± 0.3	1.7 ± 0.3

Data are LS mean ± standard error, unless otherwise indicated, and from LOCF, unless otherwise indicated. $p > 0.05$ for all treatment comparisons and subgroup-by-treatment interactions. FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IGlar, insulin glargine; LOCF, last observation carried forward (endpoint); LS, least squares; LY IGlar, LY2963016 insulin glargine; s.d., standard deviation; SMBG, self-monitored blood glucose.

*Full analysis set, N numbers reflect maximum sample size.

†By SMBG.

‡Events/patient/1 year. The overall rate at 24 weeks accounts for all events reported during the 24-week treatment period.

§Including events with blood glucose ≤70 mg/dl.

were similar between the treatment groups. Adverse events reported for LY IGlar were similar to those for IGlar and were consistent with the AE profile reported in studies assessing efficacy and safety of IGlar in adult patients with T1D and T2D [30,31]. The incidences of allergic reactions and of injection site AEs were low and similar between the treatment groups. The proportion of patients with detectable anti-insulin antibodies was low and consistent with previous findings in patients with T2D [6]. Finally, median antibody percent binding was similar between treatment groups at endpoint.

The double-blind design strengthened the present study. Blinding eliminates the possibility of investigator bias and participant bias, which could affect dose titration, AE and hypoglycaemia reporting, making conclusions regarding efficacy and safety more straightforward and reliable. Another strength of this study was the inclusion of both insulin-naïve patients and previous IGlar users, which enabled us to make informative observations in both types of patients. Although randomization was not stratified by prestudy basal insulin status, the number of patients who were insulin-naïve or who were previous IGlar users was balanced between the treatment groups. For the primary and secondary objectives, data were not analysed separately because the study was powered to demonstrate non-inferiority based on the total number of patients, inclusive of both insulin-naïve and previous IGlar users; however, because there was interest in possible differential treatment effects for patients who were insulin-naïve and those who were previous IGlar users, subgroup analyses were performed to assess the consistency of the treatment effect on outcomes. There were no treatment-by-subgroup interactions for change in HbA1c from baseline to endpoint, indicating no significant differential treatment effects on the change in HbA1c across the subgroups; however, not surprisingly, baseline HbA1c was lower in the group previously treated with IGlar versus the insulin-naïve group, and the improvement in HbA1c was greater in the insulin-naïve versus the group previously treated with IGlar. No significant differential treatment effects in these subgroups were seen in other endpoints including proportion of patients reaching target HbA1c, FPG, insulin dose, hypoglycaemia rate and weight change. The observed responses and outcomes in both treatment groups were generally consistent with findings in other studies of insulin-naïve and previously insulin-treated patients with T2D treated with insulin glargine [3,6,32], although to our knowledge, no studies to date have examined endpoints in these subgroups within the same study.

While the duration of the present study was shorter, the findings are consistent with the ELEMENT 1 study, which showed LY IGlar's similarity with IGlar with repeated once-daily dosing, over 24 and up to 52 weeks, in patients with T1D [22].

In conclusion, both LY IGlar and IGlar, when used in combination with ≥2 oral antihyperglycaemic medications, provided effective glucose control with similar safety profiles in patients with T2D. The results of this double-blind, treat-to-target

Table 4. Adverse events, allergic reactions and injection-site reactions.

AEs*	LY IGlar N = 376†	IGlar N = 380†
Deaths	1 (<1)	1 (<1)
SAEs	15 (4)	18 (5)
Discontinuations due to an AE	6 (2)	11 (3)
Injection site AE	13 (4)	11 (3)
AEs	196 (52)	184 (48)
AE possibly related to study drug	26 (7)	23 (6)
AE possibly related to study procedure	6 (2)	8 (2)
AE possibly related to study disease state (diabetes)	19 (5)	18 (5)
Special topic assessment of allergic reactions	21 (6)	27 (7)
Pruritus, rash, dermatitis, other‡	8 (2)	12 (3)
Arthraglia, periarthritis	7 (2)	9 (2)
Injection site (reaction, pruritis, induration)	5 (1)	4 (1)
Asthma, nasal oedema	3 (1)	5 (1)
Injection site reaction (patient questionnaires)	13 (4)	11 (3)
Pain	10 (3)	5 (1)
Pruritus	4 (1)	4 (1)
Rash	3 (1)	3 (1)

Data are n (%). $p > 0.05$ for all treatment comparisons [with the exception of injection site reactions (patient questionnaires) where treatment comparisons were not performed]. AE, adverse event; IGlar, insulin glargine; LY IGlar, LY2963016 insulin glargine; SAE, serious adverse event.
*Patients may be counted in >1 category.
†Full analysis set, N numbers reflect maximum sample size.
‡Angioedema, macular rash, papular rash, pruritic rash, vesicular rash.

clinical trial showing effective glucose-lowering and similar safety and efficacy profiles for LY IGlar and IGlar in the total study population, as well as in both insulin-naïve and previously insulin-treated subgroups of patients with T2D, add to the totality of the evidence showing the similarity of LY IGlar to IGlar. LY IGlar provides a well-tolerated and effective once-daily basal insulin option for treatment of patients with T2D in combination with oral agents.

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Conflict of Interest

J. R. has served on scientific advisory panels, served as a consultant and received research support from insulin manufacturers Eli Lilly and Company, Sanofi and Novo Nordisk. P. H. has served on scientific advisory panels for Johnson & Johnson, Merck, Novo Nordisk and Roche Pharmaceuticals. A. B. has received research support from Abbvie, AstraZeneca Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc., Duke Clinical Research Institute, Eli Lilly and Company, Halozyme Therapeutics, Jaeb, Mylan, Novo Nordisk Inc., Orexigen Therapeutics Inc., Sanofi-Aventis, University of Oxford. L. L. I., W. J. H, J. S. Z., R. K. P. and M. J. P. are employees of and hold stock in Eli Lilly and Company.

J. R., P. H. and A. B. contributed to the interpretation and discussion of the research, participated in conducting the study and reviewed and edited the manuscript. W. J. H. participated in the study design, designed and conducted the statistical analyses, participated in the interpretation and discussion of the research and in writing the manuscript. L. L. I., J. S. Z., R. K. P. and M. J. P. 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. 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. M. C. (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. Study design. IGlar, insulin glargine; LY IGlar, LY2963016 insulin glargine; OAMs, oral antihyperglycaemic medications; QD, once-daily administration. *Telephone visits.

Figure S2. Patient disposition. IGlar, insulin glargine; LY IGlar, LY2963016 insulin glargine.

File S1. List of ELEMENT 2 investigators.

Table S1. Patient demographics and baseline characteristics for patients who entered the study on insulin glargine and for insulin-naïve patients.

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