basaglar®

insulin glargine injection
100 Units/mL

The BASAGLAR ELEMENT 1 clinical study

Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab*. 2015;17:726-733.

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INDICATION

BASAGLAR is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

LIMITATION OF USE

BASAGLAR is not recommended for the treatment of diabetic ketoacidosis.

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

BASAGLAR is contraindicated during episodes of hypoglycemia, and in patients with hypersensitivity to insulin glargine or one of its excipients.

Please see Important Safety Information on pages 3 and 4, and Full Prescribing Information, including Patient Information.

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ELEMENT 1 trial design[1,2]

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A 52-week phase 3, randomized, open-label study of 535 adult patients with type 1 diabetes who were also treated with insulin lispro

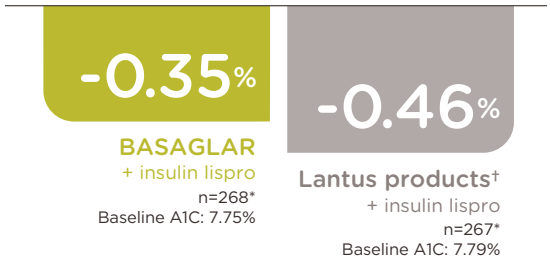
PRIMARY ENDPOINT: noninferiority of BASAGLAR to Lantus® (insulin glargine injection) products (approved in the US or outside the US) as measured by change in A1C from baseline at 24 weeks.

SECONDARY ENDPOINT: proportion of patients achieving A1C <7% at 24 weeks.

STARTING DOSE: Patients started on the same dose of BASAGLAR or U.S.- or non-U.S.-approved Lantus and at the same time of day as their prestudy basal insulin; mealtime insulin was replaced with insulin lispro at doses equivalent to prestudy mealtime insulin; titration was investigator-driven based on self-measured fasting plasma glucose to achieve glycemic targets (A1C <7%, fasting plasma-equivalent glucose ≤108 mg/dL, and other preprandial capillary blood glucoses 70 to 130 mg/dL).[1]

Type 1 diabetes: comparable A1C results[1,2]

Type 1 diabetes: change in A1C from baseline at 24 weeks



Difference of 0.108% (95% CI -0.002 to 0.219)
Noninferiority margin 0.4% and then 0.3%

* One patient randomized to the BASAGLAR group was not included in the full analysis set. Observed A1C data at 24 weeks were available from 256 (96%) and 258 (97%) patients randomized to the BASAGLAR and US- or non-US-approved Lantus groups, respectively.

†Approved in the US or outside the US
CI=confidence interval

BASAGLAR vs Lantus products (approved in the US or outside the US): percentage of patients achieving A1C <7% at 24 weeks[2]*

- **34.5%** of patients taking BASAGLAR (n=268†; baseline A1C: 7.75%)
- **32.2%** of patients taking Lantus products (approved in the US or outside the US) (n=267†; baseline A1C: 7.79%)

*Secondary endpoint.
†Full analysis set; n values represent maximum sample size.

IMPORTANT NOTE ABOUT THESE RESULTS: Above percentages of patients achieving A1C <7% at 24 weeks are derived from the BASAGLAR US Prescribing Information.[2] The published ELEMENT 1 study reported 35% for patients taking BASAGLAR vs 32% for those on Lantus products (approved in the US or outside the US).[1] These differences are due to rounding.

Please see Important Safety Information on pages 3 and 4, Full Prescribing Information, including Patient Information.

Adverse events

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This trial was not designed to evaluate the relative safety between BASAGLAR and Lantus products (approved in the US or outside the US), and comparator adverse event rates are not an adequate basis for comparison of rates between the products.

BASAGLAR vs Lantus products (approved in the US or outside the US): severe symptomatic hypoglycemia over 52 weeks of treatment[1]

*Full analysis set; n values reflect maximum sample size.
†Approved in the US or outside the US.

Hypoglycemia was the most commonly observed adverse reaction in patients using insulin, including BASAGLAR. Hypoglycemia was defined as blood glucose ≤3.9 mmol/L (≤70 mg/dL) or a sign or symptom associated with hypoglycemia. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia that required assistance of another person, and was associated with either blood glucose levels below 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.[1,2]

Rates of reported hypoglycemia depend upon the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic factors. For these reasons, comparing rates of hypoglycemia in clinical trials for BASAGLAR with the incidence of hypoglycemia for other products may be misleading, and may not be representative of hypoglycemia rates that will occur in clinical practice.

Type 1 diabetes: adverse reactions occurring in ≥5% of adult patients treated with BASAGLAR or Lantus products* over 52 weeks of treatment[2,3]

	BASAGLAR + insulin lispro (n=268)	Lantus products* + insulin lispro (n=267)
Infection†‡	24%	24%
Nasopharyngitis	16%	17%
Upper respiratory tract infection	8%	8%

*Approved in the US or outside the US.
†Infections other than nasopharyngitis or upper respiratory tract infection.
‡Infections were a category of treatment-emergent adverse events that were reported during the 52-week trial and included events such as influenza, urinary tract infection, bronchitis, gastroenteritis, and sinusitis. Excluded were nasopharyngitis and upper respiratory tract infection.[4]

IMPORTANT NOTE ABOUT THESE RESULTS: BASAGLAR adverse reactions listed above are taken from the BASAGLAR US Prescribing Information.[2] The published ELEMENT 1 study reported 16.4% of patients taking BASAGLAR experienced nasopharyngitis and 8.0% upper respiratory tract infection.[1] These differences are due to rounding. Infections other than nasopharyngitis or upper respiratory tract infection were not reported in the publication. Adverse reactions may be reported and categorized differently within the publication compared with the BASAGLAR US Prescribing Information. Although these data were collected during the study, the adverse reactions from Lantus products (approved in the US or outside the US) listed above are not included in the BASAGLAR US Prescribing Information.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

BASAGLAR is contraindicated during episodes of hypoglycemia, and in patients with hypersensitivity to insulin glargine or one of its excipients.

WARNINGS AND PRECAUTIONS

BASAGLAR KwikPen® must never be shared between patients, even if the needle is changed. Sharing poses a risk of transmission of blood borne pathogens.

Please see Important Safety Information above and on page 4, and Full Prescribing Information, including Patient Information.

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100 Units/mL

WARNINGS AND PRECAUTIONS (cont'd)

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments of concomitant anti-diabetic products may be needed.

Hypoglycemia is the most common adverse reaction associated with insulins, including BASAGLAR. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death.

Accidental mix-ups between another insulin glargine product (100 units/mL) and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between BASAGLAR and other insulins, instruct patients to always check the insulin label before each injection.

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including BASAGLAR. If hypersensitivity reactions occur, discontinue BASAGLAR; treat per standard of care and monitor until symptoms and signs resolve. BASAGLAR is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or one of the excipients.

All insulin products, including BASAGLAR, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated.

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. These patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of TZD must be considered.

ADVERSE REACTIONS

Adverse reactions commonly associated with insulin glargine products (5% or greater incidence) are: hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, edema, and weight gain.

DRUG INTERACTIONS

Certain drugs may affect glucose metabolism, requiring insulin dose adjustment and close monitoring of blood glucose. The signs and symptoms of hypoglycemia may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with BASAGLAR.

BV HCP ISI 24JUN2016

References: 1. Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab*. 2015;17:726-733. **2.** Basaglar [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company. **3.** Data on file, Lilly USA, LLC. BAS20151103E. **4.** Data on file, Lilly USA, LLC. BAS20160811A.

For more information, please see Full Prescribing Information, including Patient Information.

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Diabetes, Obesity and Metabolism 17: 726–733, 2015.

ORIGINAL ARTICLE

Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study

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[4] *Eli Lilly and Company, Indianapolis, IN, USA*

Aims: To compare the efficacy and safety of LY2963016 insulin glargine (LY IGlar) and the reference product (Lantus®) insulin glargine (IGlar) in patients with type 1 diabetes (T1D).

Methods: This phase III, randomized, open-label, 52-week study enrolled patients with T1D [glycated haemoglobin (HbA1c) ≤11%] being treated with basal (once-daily) and bolus insulin. Patients were randomized to receive once-daily LY IGlar (n = 268) or IGlar (n = 267) in combination with mealtime insulin lispro for 52 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 the non-inferiority criteria compared with IGlar for change in HbA1c from baseline to 24 weeks [−0.35 vs −0.46%, least-squares mean difference 0.108% (95% confidence interval −0.002 to 0.219), $p > 0.05$]. There were no significant ($p > 0.05$) treatment differences in other efficacy measures, including proportion of patients reaching HbA1c <7%, daily mean blood glucose, and insulin dose at 24 and 52 weeks. At 52 weeks, similar findings were observed between LY IGlar and IGlar for safety outcomes, including adverse events, allergic reactions, hypoglycaemia, weight change and insulin antibodies.

Conclusions: Both LY IGlar and IGlar, when used in combination with mealtime insulin lispro, provided effective and similar glucose control and similar safety profiles.

Keywords: LY2963016, insulin glargine, type 1 diabetes

Date submitted 13 February 2015; date of first decision 10 March 2015; date of final acceptance 11 May 2015

Introduction

Since the introduction of recombinant human insulin (Humulin®, Eli Lilly and Company, Indianapolis, IN, USA) in 1982 as the first biopharmaceutical in clinical use [1], hundreds of biopharmaceuticals have received regulatory approval [2]. Similar biological medicinal products, referred to as 'biosimilars' in regions where such a regulatory designation applies, have become available when patents for the reference product have expired (e.g. epoetin alfa, somatotropin, filgrastim and infliximab) [2,3]. Earlier attempts to introduce biosimilar human insulin products in Europe have been unsuccessful [4,5], highlighting not only the complexity and challenges of developing a biosimilar insulin, but also the standards expected. LY2963016 (LY IGlar) is the first biosimilar insulin approved for marketing authorization in the European Union (September 2014) [6]. In the USA, Lantus®, an insulin glargine (IGlar) of rDNA origin (Sanofi-Aventis, Paris, France), the reference product for LY IGlar, was approved through the new drug application pathway [7], which necessitated the filing of LY IGlar through the 505(b)(2) regulatory pathway [8], and not the 351(k) biosimilar pathway [9]; therefore, LY IGlar is not considered a biosimilar in the USA.

The new LY IGlar is a long-acting human insulin analogue with an identical amino acid sequence and the same pharmaceutical form and strength as the reference product IGlar [10]. In 2000, IGlar was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for once-daily subcutaneous administration for the treatment of type 1 diabetes (T1D) and type 2 diabetes (T2D) [11]. In T1D, IGlar has been shown to provide similar glycaemic control to NPH, with either lower or similar rates of hypoglycaemia [12,13].

Because of the complexity of biotechnology-derived insulin products, the principles and procedures involved in the approval of chemically derived generic medicines are not appropriate. Specific guidelines from regulatory agencies outline the data requirements for establishing similarity with a

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marketed biological product [14–17]. The scientific principles in demonstrating similarity of LY IGlar to IGlar are consistent with these guidelines and requirements for demonstrating similarity between two biological products. The LY IGlar development programme therefore includes chemical and biophysical characterization, non-clinical pharmacodynamics (PD) and toxicological studies, as well as clinical studies to evaluate pharmacokinetics (PK) and PD, efficacy and safety, including immunogenicity.

Non-clinical physicochemical, biological characterization and toxicological [18] comparisons of LY IGlar with IGlar were submitted to regulatory agencies. The EMA found the quality of LY IGlar to be acceptable when used in accordance with the label [10], and concluded that similarity between LY IGlar and IGlar has been satisfactorily demonstrated from the quality perspective [10]. Euglycaemic clamp studies in healthy volunteers indicated similar PK and PD properties of LY IGlar and IGlar [19,20]. Similar PD effects and duration of action were demonstrated for LY IGlar and IGlar in a small group of subjects with T1D [21].

The safety and efficacy of LY IGlar have been assessed in randomized clinical trials in patients with T1D and T2D. LY IGlar compared with IGlar in combination with oral antihyperglycaemic medications provided equivalent efficacy and similar safety profiles, with no clinically meaningful differences in patients with T2D [22]. The present paper reports on the clinical trial that compares the efficacy and safety of LY IGlar and IGlar with mealtime insulin lispro in patients with T1D during a 52-week treatment period.

Methods

Study Design and Patients

This phase III, randomized, multinational, multicentre, two-arm, active-controlled, open-label, parallel study had a 24-week treatment period for the primary efficacy endpoint, a 28-week extension (with a resulting 52-week safety endpoint), and a 4-week post-treatment follow-up (Figure S1). The primary objective was to show the non-inferiority of LY IGlar once-daily compared with IGlar once-daily, as measured by change in glycated haemoglobin (HbA1c), from baseline to 24 weeks, when used in combination with premeal insulin lispro administered three times daily in patients with T1D. 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 ClinicalTrials.gov under the number: NCT01421147. The ELEMENT 1 study investigators are listed in File S1.

Inclusion criteria included T1D duration of ≥1 year, age ≥18 years, receiving basal-bolus insulin therapy for ≥1 year before screening, HbA1c ≤11.0% and body mass index ≤35 kg/m^2. Exclusion criteria included treatment with a biosimilar IGlar, oral antihyperglycaemic medications, recent twice-daily IGlar treatment, pramlintide, or continuous subcutaneous insulin infusion, total daily insulin dose ≥1.5 U/kg, or ≥1 episode of severe hypoglycaemia or emergency room visit or hospitalization for poor glucose control within the past 6 months. The prestudy basal-bolus regimen was required to be a once-daily basal insulin injection of NPH, IGlar, or detemir for ≥3 months (≥90 days) before screening, combined with mealtime injections of human regular insulin, insulin analogue lispro, aspart or glulisine.

Treatment assignment was stratified by country, HbA1c value (<8.5, ≥8.5%), and time of basal insulin injection (daytime, evening/bedtime). Patients were randomized to receive LY IGlar once-daily or IGlar once-daily with mealtime insulin lispro for 24 weeks, at which time the primary efficacy endpoint of change in HbA1c levels from baseline was assessed. Patients continued to receive their assigned treatment for an extended period of 28 weeks (total duration of 52 weeks). Clinic visits occurred at screening, randomization (week 0), and weeks 2, 6, 12, 18, 24, 30, 36, 44 and 52 (Figure S1).

Patients were randomized to LY IGlar or IGlar and started on the same dose at the same time of day as their prestudy basal insulin. At randomization, all patients' mealtime insulins were replaced with insulin lispro at doses equivalent to their prestudy mealtime insulin, as determined by unit-to-unit conversion. All patients had adjustments of basal insulin (LY IGlar or IGlar) that were primarily investigator-driven during phone and office visits. Insulin dose adjustments were carried out in both treatment groups to help patients achieve glycaemic targets [HbA1c <7%, fasting plasma glucose (FPG) ≤6.0 mmol/l (108 mg/dl), and other preprandial capillary blood glucoses 3.9–7.2 mmol/l (70–130 mg/dl)], while minimizing/avoiding hypoglycaemia. While dosage adjustments were to be completed by week 12, adjustments after week 12 were made for safety concerns, such as hypoglycaemia or unacceptable hyperglycaemia as determined by the investigator.

Outcomes

The HbA1c analyses were conducted at 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 (premeal 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 fasting plasma glucose (FPG) variability was calculated based on the standard deviation of the morning premeal blood glucose value. Data on adverse events (AEs), defined as events that were reported as new or worsening in severity after randomization, were collected at every visit. Clinical chemistry and haematology panels were collected at baseline, weeks 24 and 52. 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 detectable binding to LY IGlar. Sensitivity was 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 having 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 assistance of another person to actively administer treatment or other resuscitative actions. All severe hypoglycaemic 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 was in accordance with regulatory requirements [24–26]. 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, 184 (368 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 0.884% for change from baseline in HbA1c, a two-sided significance level of 0.05, and 90% power for a 0.3% NIM and >99% power for a 0.4% NIM. Assuming a 15% drop-out rate at 24 weeks, the required number of randomized patients was 216 per arm (432 total).

All analyses were conducted using SAS version 9.2 (SAS Drug Development system, Cary, NC, USA) and were based on all randomized patients who 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 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. No adjustments for multiplicity were performed.

The primary efficacy outcome measure was the change in HbA1c from baseline to the 24-week endpoint. The primary analysis model was an analysis of covariance (ANCOVA) with country, time of basal insulin injection (daytime, 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 I 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%. If LY IGlar was declared non-inferior to IGlar in the primary treatment comparison and IGlar was declared non-inferior to LY IGlar in the secondary treatment comparison, then LY IGlar was considered to have equivalent efficacy as 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 (<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.

Table 1. Patient demographics and baseline characteristics.

Measurement	LY IGlar N = 268*	IGlar N = 267*
Age (years)	41 ± 14	41 ± 13
Male, n (%)	155 (58)	155 (58)
Race, n (%)		
American-Indian or Alaska native	11 (4)	12 (5)
Asian	49 (18)	51 (19)
Black or African-American	9 (3)	2 (1)
Multiple	1 (<1)	1 (<1)
White	197 (74)	201 (75)
Body weight, kg	76 ± 17	75 ± 15
BMI, kg/m^2	26 ± 4	25 ± 4
Duration of diabetes, years	16 ± 11	17 ± 11
Basal insulin, n (%)		
IGlar	218 (81)	234 (88)
Other	50 (19)†	33 (12)‡
Insulin dose		
Basal, U/day	25.1 ± 12.9	23.3 ± 11.6
Basal, U/kg/day	0.33 ± 0.14	0.31 ± 0.13
Prandial, U/day	30.5 ± 16.7	29.5 ± 16.7
Prandial, U/kg/day	0.40 ± 0.19	0.40 ± 0.22
HbA1c		
%	7.75 ± 1.13	7.79 ± 1.03
mmol/mol	61 ± 12	62 ± 11
Entry HbA1c, n (%)		
<8.5% (<69 mmol/mol)	190 (71)	186 (70)
<7.0% (<53 mmol/mol)	73 (27)§	49 (18)
FPG by SMBG		
mmol/l	8.37 ± 3.01	8.19 ± 2.99
mg/dl	151 ± 54	147 ± 54
Daily mean blood glucose by SMBG		
mmol/l	8.65 ± 2.07	8.71 ± 1.91
mg/dl	156 ± 37	157 ± 34
% insulin antibody binding (median)	0.69	0.88

$p > 0.05$ for all treatment comparisons except where indicated. Data are mean ± standard deviation, unless otherwise indicated. BMI, body mass index; 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.

†Insulin detemir, n = 24, 9.0%; NPH insulin, n = 26, 9.7%.

‡Insulin detemir, n = 20, 7.5%; NPH insulin, n = 13, 4.9%.

§$p < 0.05$ vs IGlar.

Results

Patients

Of the 535 patients included in the full analysis set population, 95% completed the 24-week treatment period and 92% completed the 52-week study. Withdrawal by the participant

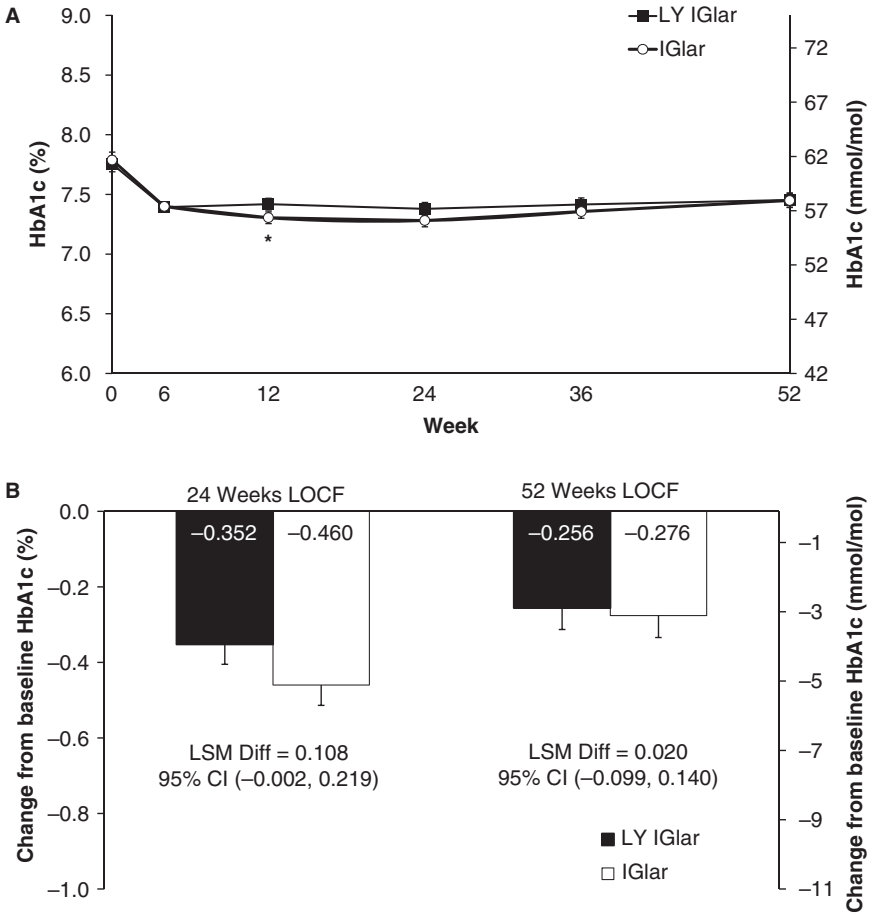

Figure 1. (A) Change in absolute glycated haemoglobin (HbA1c) over 52 weeks. (B) Change from baseline HbA1c at 24 weeks LOCF and 52 weeks LOCF. Data are least squares mean ± standard error. Open circles: insulin glargine (IGlar); closed squares: LY2963016 insulin glargine (LY IGlar). *p = 0.030 for treatment difference at week 12.

was the most common reason for study discontinuation in both groups (Figure S2). Patient demographics for both groups were well balanced, except for more patients entering the study with HbA1c levels <7.0% in the LY IGlar versus IGlar group (Table 1).

Efficacy

Both treatment groups had within-group significant ($p < 0.001$) decreases in least squares (LS) mean HbA1c values from baseline, which began at week 6 and continued through the 52-week endpoint (LOCF; Figure 1A). Except for HbA1c (LS mean) at week 12 [IGlar 7.31% (56 mmol/mol) vs LY IGlar 7.42% (58 mmol/mol); $p = 0.03$], there were no statistically significant treatment differences at any other time point (Figure 1A). The primary objective was met, demonstrating 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 NIM was also demonstrated (Figure 1B, Table 2). Collectively, the non-inferiority results indicate that LY IGlar and IGlar have equivalent efficacy. LY IGlar and IGlar continued to have similar efficacy based on the change in HbA1c from baseline to the 52-week endpoint (LOCF) (Figure 1B, Table 2). At the 24- and 52-week endpoints (LOCF), proportions of patients achieving target HbA1c values <7.0 and ≤6.5% were not statistically significantly different between treatment groups (Table 2). A *post hoc* analysis, adjusting for baseline differences, showed no significant treatment differences in the proportion of patients achieving HbA1c <7.0% at the 24-week, and the 52-week endpoint (LOCF; data not shown).

Figure S3 shows the seven-point mean SMBG values at baseline, 24 weeks LOCF and 52 weeks LOCF. No statistically significant treatment differences were observed for any SMBG time point, including morning premeal (FPG), at the 24- and 52-week endpoints (LOCF), except for the small differences at the following time points: bedtime (24- and 52-week endpoints) and 03:00 hours (24-week endpoint), where blood glucose values were statistically significantly lower in the LY IGlar than in the IGlar group.

Daily mean blood glucose measurements at baseline (Table 1), 24 weeks LOCF and 52 weeks LOCF were similar between treatment groups (Table 2). Fasting glucose variability was similar at all time points, with the exception of the following: lower in the LY IGlar versus IGlar group at week 6 {LS mean [standard error (s.e.)] difference −0.42 (0.14) mmol/L;

Table 2. Clinical assessments.

Measurement	24 weeks		52 weeks	
	LY IGlar N = 268*	IGlar N = 267*	LY IGlar N = 268*	IGlar N = 267*
HbA1c, %				
Endpoint	7.42 ± 0.05	7.31 ± 0.05	7.52 ± 0.06	7.50 ± 0.06
Change from baseline	−0.35 ± 0.05	−0.46 ± 0.05	−0.26 ± 0.06	−0.28 ± 0.06
LSM Diff (95% CI)	0.108 (−0.002, 0.219)		0.020 (−0.099, 0.140)	
HbA1c, mmol/mol				
Endpoint	58 ± 1	56 ± 1	59 ± 1	58 ± 1
Change from baseline	−4 ± 1	−5 ± 1	−3 ± 1	−3 ± 1
LSM Diff (95% CI)	1.2 (−0.1† 2.4)		0.2 (−1.1, 1.5)	
HbA1c, n (%)				
<7% (<53 mmol/mol)	92 (35)	86 (32)	81 (30)	67 (25)
≤6.5% (≤48 mmol/mol)	54 (20)	49 (18)	42 (16)	36 (14)
Daily mean blood glucose				
mg/dl	150 ± 2	150 ± 2	149 ± 2	153 ± 2
mmol/l	8.32 ± 0.13	8.31 ± 0.13	8.29 ± 0.13	8.51 ± 0.14
FPG by SMBG				
mg/dl	144 ± 4	141 ± 4	145 ± 4	149 ± 4
mmol/l	7.98 ± 0.20	7.81 ± 0.20	8.03 ± 0.20	8.29 ± 0.21
Insulin dose				
Basal, U/day	27.77 ± 0.97	26.05 ± 0.99	28.46 ± 1.07	26.40 ± 1.09
Basal, U/kg/day	0.37 ± 0.01	0.36 ± 0.01	0.38 ± 0.01	0.36 ± 0.01
Prandial, U/day	26.34 ± 1.35	25.07 ± 1.36	27.80 ± 1.33	27.10 ± 1.34
Prandial, U/kg/day	0.35 ± 0.02	0.35 ± 0.02	0.37 ± 0.02	0.37 ± 0.02
Body weight, kg	74 ± 1	73 ± 1	74 ± 1	73 ± 1
Mean ± s.d. hypoglycemia rate overall‡, events/patient/year				
Total	86.5 ± 77.3	89.2 ± 80.1	77.0 ± 68.7	79.8 ± 74.5
Nocturnal	18.3 ± 23.6	18.4 ± 21.5	16.1 ± 20.2	17.3 ± 19.5
Severe	0.06 ± 0.52	0.09 ± 0.50	0.07 ± 0.46	0.08 ± 0.46
Patients with detectable antibodies overall§, n (%)	80 (30)	90 (34)	107 (40)	105 (39)
% insulin antibody binding (median)	1.17	1.10	0.92	0.89

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

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

†0.1 mmol/mol is the equivalent of 0.01% (the National Glycohemoglobin Standardization Program converter tool will not convert values lower than 0.01).

‡The overall rate at 24 and 52 weeks accounts for all events reported during the 24-week treatment period, and all events reported during the 52-week study (treatment and extension periods), respectively.

§Measured for the overall 24-week treatment period and for the overall 52-week study period and not at LOCF.

p = 0.004} and week 52 [LS mean (s.e.) difference −0.31 (0.14) mmol/L; p = 0.027].

There were no statistically significant differences between treatment groups in basal insulin dose or prandial insulin dose at the 24- or 52-week endpoints [LOCF; U/day or U/kg/day (Table 2, Figure S4A)]. The increases in LS mean daily basal insulin dose from baseline to endpoints (LOCF) were similar in both treatment groups (24 weeks LOCF: LY IGlar 0.023 U/kg/day, IGlar 0.027 U/kg/day, p = 0.573; 52 weeks LOCF: LY IGlar 0.031 U/kg/day; IGlar 0.030 U/kg/day, p = 0.976), although the degree of basal insulin dose adjustment (change from baseline) slightly differed between the treatments at some time points before the 24-week endpoint (Figure S4B).

There were no statistically significant differences between treatment groups for actual mean body weight at baseline (Table 1) or endpoints (LOCF; Table 2). The LS mean increases from baseline to the 24-week endpoint (LOCF) were 0.36 and 0.12 kg in the LY IGlar and IGlar groups, respectively; increases at the 52-week endpoint (LOCF) were 0.71 and 0.36 kg, respectively.

Safety

There were no statistically significant differences between treatment groups for the rate of each category of hypoglycaemia, adjusted for 1 year, at 24 or 52 weeks (Table 2). Similar rates of documented symptomatic hypoglycaemia (blood glucose ≤3.9 mmol/l [≤70 mg/dl]) were seen between groups at 24 weeks (p = 0.231) and 52 weeks (p = 0.319). Similarly, there were no significant treatment differences in the incidence of total hypoglycaemia for 24 weeks (LY IGlar 94%, IGlar 95%; p = 0.703) or for 52 weeks (LY IGlar 96%, IGlar 97%; p = 0.495), in the incidence of nocturnal hypoglycaemia for 24 weeks (LY IGlar, 82%; IGlar, 80%, p = 0.661) or for 52 weeks (LY IGlar 86%, IGlar 88%; p = 0.606), and in the incidence of

Table 3. Adverse events, allergic reactions and injection site reactions.

AEs*	LY IGlar	IGlar
Deaths	0 (0)	1 (<1)
SAEs	20 (8)	24 (9)
Discontinuations due to an AE	2 (1)	6 (2)
Injection site AE	7 (3)	3 (1)
AEs	167 (62)	166 (62)
AE possibly related to study drug	17 (6)	14 (5)
AE possibly related to study procedure	2 (1)	2 (1)
AE possibly related to study disease state (diabetes)	21 (8)	16 (6)
Special topic assessment of allergic reactions	20 (8)	11 (4)
Pruritus, rash, dermatitis, other†	7 (3)	4 (2)
Arthralgia, arthritis	4 (2)	5 (2)
Injection site (reaction, induration, nodule, swelling)	6 (2)	2 (1)
Drug hypersensitivity and hypersensitivity	1 (<1)	1 (<1)
Allergic respiratory symptom, asthma	2 (1)	0 (0)
Injection site reaction (patient questionnaires)	7 (3)	3 (1)
Pain	6 (2)	2 (1)
Pruritus	2 (1)	1 (<1)
Rash	2 (1)	1 (<1)

$p > 0.05$ for all treatment comparisons; treatment comparisons were not performed if there were <4 patients with events. Data are n (%). AE, adverse event; IGlar, insulin glargine; LY IGlar, LY2963016 insulin glargine; SAE, serious adverse event.

*Patients may be counted in >1 category.

†Photosensitivity reaction, urticaria.

severe hypoglycaemia for 24 weeks (LY IGlar 2%, IGlar 3%; $p = 0.174$) or for 52 weeks (LY IGlar 4%, IGlar 4%; $p = 0.828$).

Table 3 contains an overview of AEs reported during the 52-week study. The incidences of AEs and SAEs reported for LY IGlar were similar to those of IGlar. The most frequently reported AEs were nasopharyngitis (16.4%), upper respiratory tract infection (8.0%), hypoglycaemia (4.7%) and diarrhoea (4.1%). In both treatment groups, the majority of AEs were of mild severity. There was one death as a result of hypertrophic cardiomyopathy (IGlar-treated) which was not considered by the investigator to be related to study drug or study procedures. The incidence of allergic reactions was low in both treatment groups; most events were mild in severity, and none led to discontinuation (Table 3). 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 3).

A total of 212 participants (39.8%) had detectable antibodies to insulin and there was no statistically significant difference between treatment groups at 24 or 52 weeks (Table 2). No statistically significant differences between treatment groups in median insulin antibody binding values were observed at the 24- and 52-week endpoints (LOCF; Table 2). No clinically meaningful baseline to endpoint changes in any laboratory values were identified within and between groups (data not shown).

Discussion

In addition to analytical studies, clinical trials need to be conducted to confirm the efficacy findings from the PK and PD studies and, more importantly, to evaluate safety, including immunogenicity. Biological copies of human insulins and certain insulin analogues (including IGlar) are available in countries where current regulations for similar biological products are less stringent [27]. While there are publications on biosimilars in general, our findings address a gap in evidence-based knowledge of biosimilar insulins.

The present phase III trial in patients with T1D shows that LY IGlar is non-inferior to IGlar, as measured by change in HbA1c from baseline to 24 weeks when used in combination with mealtime lispro, and conversely that IGlar is non-inferior to LY IGlar. Both treatment groups were efficacious in improving glycaemia with similar lowering of blood glucose levels from baseline to the 24- and 52-week endpoints of the study, with similar changes in insulin dose and weight. LY IGlar was well tolerated, with a similar safety profile to that of IGlar.

The demonstration of non-inferiority is in accordance with FDA and EMA guidances [24–26]. The prespecified criteria for showing equivalent efficacy between LY IGlar and IGlar were also met. Similar HbA1c levels were noted between treatment groups from the 24-week endpoint through the remainder of the study. Similar proportions of patients treated with LY IGlar and IGlar achieved an HbA1c target of <7%, and remained similar after adjusting for differences at baseline. SMBG profiles were similar between treatment groups except for some small but statistically significant differences at certain time points which were not considered clinically meaningful based on similar mean daily blood glucose and the similar occurrence of hypoglycaemia in the LY IGlar and IGlar groups. Fasting glucose variability was similar between treatment groups except for a few time points at which there was statistically lower variability with LY IGlar. No significant treatment differences were seen in insulin dose and weight.

The 28-week extension period was necessary for the collection of safety data, including immunogenicity data up to 52 weeks. The results did not show any significant differences in safety measures between the treatment groups. There were no statistically significant treatment differences for the incidence or rate of hypoglycaemia for any category of hypoglycaemia. AEs reported for LY IGlar were similar to those reported for IGlar, and were consistent with the AE profile reported in studies assessing the efficacy and safety of IGlar in adult patients with T1D and T2D [28,29]. Allergic reactions and injection site AEs, which were analysed to assess any potential hypersensitivity reactions, were similar between treatment groups. Similar proportions of patients had detectable anti-insulin antibodies and median antibody percent binding was similar between treatment groups at endpoint.

An open-label design was chosen in order to provide efficacy and safety data using the planned insulin presentation for the product (i.e. prefilled pen device). Because of the uniqueness

and distinctiveness of the pen device, double-blinding would have involved a double-dummy design, imposing undue injection burden on patients in a relatively long duration study. The lack of blinding, in turn, may have contributed to the small but statistically significant difference in HbA1c at 12 weeks, where HbA1c was significantly lower in the IGlar treatment group. During this time, there were also non-significant differences in insulin dose adjustments during the titration period (Figure S4B). Investigators were aware of the treatment received by each patient, which may have contributed to the more aggressive dose titration from baseline to 18 weeks in the IGlar group (Figure S4B) because of greater investigator familiarity and confidence in titration of IGlar than with LY IGlar. Insulin doses between treatments were more similar during the course of the study after the titration period and there were no statistically significant treatment differences in HbA1c (or in insulin dose) at the 24-week (primary) and 52-week endpoints. Notably, in the double-blind study in patients with T2D, no between-treatment differences in insulin dose titration or HbA1c were noted [22].

In terms of generalizability of the study's findings, it may be noted that patients on twice-daily basal insulin were excluded because only once-daily administration of IGlar is approved in all of the participating countries [28,29]. Having all patients on a prestudy once-daily basal insulin regimen minimized adjustments and, together with using a common prandial insulin during the study, ensured a more homogenous study population.

In conclusion, our data show LY IGlar's similarity with IGlar with once-daily dosing, over 24 and up to 52 weeks, in a large and multinational population of patients with T1D when used with premeal insulin lispro. These findings of similar efficacy and safety are in accordance with the similar PK/PD profiles between these insulin glargine products [30] and consistent with the findings in T2D [22]. Taken together with the findings from physicochemical and preclinical studies and other clinical trials comparing LY IGlar and IGlar, the study results contribute to the totality of evidence that LY IGlar provides a well-tolerated and effective once-daily basal insulin option for treatment of patients with diabetes.

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Conflict of Interest

T. C. B. has served on speaker bureaus for Eli Lilly and Company, Merck, Novo Nordisk, Sanofi-Aventis, Astra Zeneca, Boehringer-Ingelheim, Janssen and Medtronic, has received research support from Eli Lilly and Company, Novo Nordisk, Sanofi-Aventis, Astra Zeneca, Halozyme, Merck, Janssen and Medtronic and has served on a clinical advisory board for Eli Lilly and Company and Sanofi-Aventis. D. D. has no conflicts of interest to disclose. 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. 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.

T. C. B, D. D. and J. R. contributed to the interpretation and discussion of the research, 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. L. L. I. 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. Michelle Carey (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; QD, once-daily administration. *Telephone visits.

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

Figure S3. (A) Self-monitored blood glucose (SMBG) at baseline. (B) SMBG at 24 weeks LOCF. (C) SMBG at 52 weeks LOCF. Data are least squares mean ± standard error. Open circles: insulin glargine (IGlar); closed squares: LY2963016 insulin glargine (LY IGlar). *$p < 0.05$ for treatment difference.

Figure S4. (A) Basal insulin dose (U/kg/day) over 52 weeks. (B) Change from baseline basal insulin dose (U/kg/day) over 52 weeks. Data are least squares mean ± standard error. Open circles: insulin glargine (IGlar); closed squares: LY2963016 insulin glargine (LY IGlar).

File S1. List of ELEMENT 1 investigators.

References

1. Johnson IS. Human insulin from recombinant DNA technology. Science 1983; **219**: 632–637.
2. Krämer I, Sauer T. The new world of biosimilars: what diabetologists need to know about biosimilar insulins. Br J Diabetes Vasc Dis 2010; **10**: 163–171.
3. Grabowski H, Guha R, Salgado M. Biosimilar competition: lessons from Europe. Nat Rev Drug Discov 2014; **13**: 99–100.
4. European Medicines Agency. Marvel Life-Sciences Ltd withdraws its marketing authorisation applications for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel. EMEA/2435/2008. Press Release. 2008. Available from URL: www.ema.europa.eu/docs/

en_GB/document_library/Press_release/2009/11/WC500015335.pdf. Accessed 15 October 2014.

5. European Medicines Agency. Marvel Life Sciences Ltd withdraws its marketing authorisation applications for Solumarv, Isomarv medium and Combimarv (human insulin). Press Release. 2012. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/11/WC500135156.pdf. Accessed 15 October 2014.
6. European Medicines Agency. Abasaglar (previously Abasria). 2014. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/002835/human_med_001790.jsp&mid=WC0b01ac058001d124. Accessed 31 March 2015.
7. Food and Drug Administration. Drug Approval Package: Lantus (Insulin Glargine [rDNA Origin]). NDA #21-081 2000. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21081_Lantus.cfm. Accessed 31 March 2015.
8. Eli Lilly and Company. FDA grants tentative approval for Lilly and Boehringer Ingelheim's Basaglar™ (insulin glargine injection). 2014. Available from URL: https://investor.lilly.com/releasedetail.cfm?ReleaseID=866751. Accessed 31 March 2015.
9. Food and Drug Administration. Biologics Price Competition and Innovation Act. 2009. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf. Accessed 31 March 2015.
10. European Medicines Agency. European public assessment report: Abasria. 2014. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf. Accessed 31 March 2015.
11. Hilgenfeld R, Seipke G, Berchtold H, Owens DR. The evolution of insulin glargine and its continuing contribution to diabetes care. Drugs 2014; **74**: 911–927.
12. Raskin P, Klaff L, Bergenstal R et al. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care 2000; **23**: 1666–1671.
13. Ratner RE, Hirsch IB, Neifing JL et al. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care 2000; **23**: 639–643.
14. European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. 2005. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 31 March 2015.
15. World Health Organization. Expert Committee on biological standardization. Guidelines on evaluation of Similar Biotherapeutic Products (SBPs). 2009. Available from URL: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Accessed 31 March 2015.
16. Food and Drug Administration. Guidance for industry: clinical pharmacology data to support a demonstration of biosimilarity to a reference product. 2014. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf. Accessed 31 March 2015.
17. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. 2014. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165988.pdf. Accessed 31 March 2015.
18. Byrd RA, Blackbourne JL, Schultze AE, Vahle JL. Comparative subchronic toxicity studies in rats of LY2963016 (LY), an insulin glargine product, with USA sourced Lantus® (US-L) and EU-sourced Lantus® (EU-L). Toxicologist 2014; **138**: 1650.
19. Linnebjerg H, Quin Lam EC, Seger ME et al. Comparative pharmacokinetics (PK) and pharmacodynamics (PD) of LY2963016 insulin glargine and EU- and U.S.-approved versions of Lantus® insulin glargine in healthy subjects. Diabetes 2014; **63**(Suppl. 1): 889-P.
20. Zhang X, Quin Lam EC, Seger ME et al. Comparative pharmacokinetics and pharmacodynamics of two insulin glargine products, LY2963016 and Lantus®, in healthy subjects at two dose levels. Diabetes 2014; **63**(Suppl. 1): 890-P.
21. Heise T, Zhang X, Quin Lam EC et al. Duration of action of 2 insulin glargine products, LY2963016 and Lantus®, in subjects with type I diabetes mellitus (T1DM). Diabetes 2014; **63**(Suppl. 1**)**: 891-P.
22. Rosenstock J, Hollander P, Bhargava A, Ilag LL, Pollom RK, Zielonka JS, Huster WJ, Prince MJ (2015), 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). Diabetes, Obesity and Metabolism 2015; **17**: 734–741.
23. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997; **277**: 925–926.
24. Food and Drug Administration. Guidance for industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. Draft guidance February 2008. 2008. Available from URL: http://www.fda.gov/downloads/Drugs/Guidances/ucm071624.pdf. Accessed 1 April 2015.
25. Food and Drug Administration. Guidance for industry: non-inferiority clinical trials. Draft guidance March 2010. 2010. Available from URL: http://www.fda.gov/downloads/Drugs/ … /Guidances/UCM202140.pdf. Accessed 1 April 2015.
26. European Medicines Agency. Guideline on the choice of the non-inferiority margin. 2005. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf. Accessed 15 October 2014.
27. Owens DR, Landgraf W, Schmidt A, Bretzel RG, Kuhlmann MK. The emergence of biosimilar insulin preparations-a cause for concern? Diabetes Technol Ther 2012; **14**: 989–996.
28. European Medicines Agency. LANTUS: EPAR – Product information. 2015. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000284/WC500036082.pdf. Accessed 1 April 2015.
29. U.S. National Library of Medicine. LANTUS- insulin glargine injection, solution. Drug label information. 2015. Available from URL: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d5e07a0c-7e14-4756-9152-9fea485d654a. Accessed 1 April 2015.
30. Linnebjerg H, Lam ECQ, Seger ME et al. Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and EU- and US-approved versions of Lantus® insulin glargine in healthy subjects: 3 randomized euglycemic clamp studies (under review). 2015.