Similar Efficacy and Safety of Basaglar® and Lantus® in Patients with Type 2 Diabetes in Age Groups (< 65 Years, ≥ 65 Years): A Post Hoc Analysis from the ELEMENT-2 Study

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ABSTRACT

Introduction: To compare efficacy and safety of Basaglar® [insulin glargine 100 units/mL; LY insulin glargine (LY IGlar)] to Lantus® [insulin glargine 100 units/mL; SA insulin glargine (SA IGlar)] in older (≥ 65 years) or younger (< 65 years) patients with type 2 diabetes (T2D).

Methods: This subgroup analysis of a phase 3, randomized, double-blind, multinational, 24-week study compared LY IGlar and SA IGlar on several clinical efficacy (change in glycated hemoglobin (A1c), basal insulin dose, weight) and safety outcomes (incidence of adverse events, insulin antibodies, hypoglycemia incidence and rates) in patients either ≥ 65 or < 65 years.

Results: Compared with patients aged < 65 years (N = 542), patients aged ≥ 65 years (N = 214) had a significantly longer duration of diabetes; lower baseline A1c and body weight; and body mass index; and were more likely to report prestudy SA IGlar use. Compared to patients < 65 years, patients ≥ 65 years needed a lower basal insulin dose and experienced lower body weight gain. There were no significant treatment-by-age interactions for the clinical efficacy and safety outcomes, indicating that there was no differential treatment effect (LY IGlar vs SA IGlar) for patients ≥ 65 years vs those < 65 years. Moreover, within each age subgroup, LY IGlar and SA IGlar were similar for all clinical efficacy and safety outcomes.

Conclusions: LY IGlar and SA IGlar exhibit similar efficacy and safety in patients with T2D who are ≥ 65 years and in those < 65 years.

Trial Registration: ClinicalTrials.gov trial registration: NCT01421459.

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PLAIN LANGUAGE SUMMARY

Plain language summary available for this article.

The aim of this phase 3 clinical study was to compare the efficacy and safety of two drugs, Basaglar® (LY IGlar) and Lantus (SA IGlar), in patients with type 2 diabetes that were either 65 years of age and/or older or younger than 65 years of age. This study ran for 24 weeks. The factors used to measure efficacy were changes in glycated hemoglobin (A1c), insulin dose, and weight. The safety outcomes were incidence of
adverse events, incidence and levels of insulin antibodies, and the incidence and rate of low blood sugar. Compared with patients less than 65 years of age (N = 542), patients 65 years of age and older (N = 214) had diabetes for a significantly longer time period; had a lower baseline A1c, body weight, and body mass index; and were more likely to report that they used SA IGlar prestudy. Compared to patients less than 65 years of age, patients equal to or older than 65 years of age showed significantly smaller increases in insulin dose and body weight. There were no significant treatment-by-age interactions for the efficacy and safety outcomes, indicating that there was no difference in treatment effect (LY IGlar vs SA IGlar) for patients equal to or older than 65 years of age vs those less than 65 years of age. Moreover, within each age subgroup, LY IGlar and SA IGlar were similar for all clinical efficacy and safety outcomes. LY IGlar and SA IGlar have similar efficacy and safety in patients with T2D who are equal to or older than 65 years of age and in those less than 65 years of age.

**Keywords:** Age; Efficacy; Insulin; Safety; Type 2 diabetes

**INTRODUCTION**

It is anticipated that from 2000 to 2030, the prevalence of diabetes among adults older than 64 years is expected to increase with estimates ranging from 48 million in developed countries to more than 82 million in developing countries [1]. Older adults with diabetes often present with other comorbid conditions that limit self-care abilities and impact health outcomes and quality of life [2]. Maintaining glycemic control can be challenging in this population because of cognitive deficits and increased functional decline, which may impact the ability to provide self-care [3]. Additionally, older adults are more likely to take multiple medications, which may contribute to increased risks, such as urinary incontinence, falls, and fractures [2]. Once diagnosed, many older adults with diabetes may remain under the care of a primary care provider who should customize treatment on the basis of the clinical and functional heterogeneity of this population [2, 4–6].

Insulin glargine is an initial insulin treatment option and part of basal-bolus therapy in patients with type 2 diabetes (T2D) who are not achieving glycemic control with their current treatment [7]. Older adults with T2D may benefit from insulin glargine treatment because of prolonged duration of action allowing for once-daily dosing and lower risk of hypoglycemia relative to neutral protamine Hagedorn (NPH) [8–10] or other comparators [10]. Basaglar® [insulin glargine 100 units/mL, LY insulin glargine (LY IGlar); Eli Lilly and Company, Indianapolis, IN, USA] is the first authorized biosimilar insulin in the European Union [11]. LY IGlar has an identical primary amino acid sequence to that of Lantus® [insulin glargine 100 units/mL, SA insulin glargine (SA IGlar); Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany] [11]. Both LY IGlar and SA IGlar have highly similar preclinical, efficacy, safety, and immunogenicity profiles in patients with type 1 diabetes and T2D [11–14]. To determine whether these similarities in efficacy and safety profiles of LY IGlar and SA IGlar are also true for older adults (≥ 65 years) with T2D, this subgroup analysis compared the efficacy and safety of LY IGlar to SA IGlar in patients with T2D from the ELEMENT-2 study on the basis of age (≥ or < 65 years) at study entry.

**METHODS**

**Study Design**

The ELEMENT-2 study was a phase 3, multinational, randomized, double-blind, 24-week study in patients with T2D. Details of the ELEMENT-2 study have been previously reported [11], and a post hoc study from ELEMENT-2 is reported here. The study conduct conformed to the ethical principles described in the Declaration of Helsinki [15] and written informed consent was obtained from all patients. The
The efficacy and safety of LY IGlar and SA IGlar were evaluated in patients aged ≥ 65 years and in patients aged < 65 years. Analyses were based on the full analysis set, which included all randomized patients who received at least one dose of study drug [11]. For insulin antibody level assessment, the analysis population was defined as all randomized patients who received at least one dose of study drug and had a baseline and at least one post-baseline insulin antibody level assessment [14].
RESULTS

Baseline Characteristics

Of the 756 patients enrolled, 214 (28.3%) were ≥ 65 years old and 542 (71.7%) were < 65 years old. Patients aged ≥ 65 years were more likely to be white, more likely to report prior SA IGlar use, have a significantly longer duration of diabetes, and have significantly lower A1c, body weight, and body mass index than patients < 65 years. Significantly fewer patients 65 years or older had normal renal function status. Other baseline characteristics were similar between both age subgroups (Table 1).

Efficacy

Older (≥ 65 years) and younger (< 65 years) patients in both treatment groups showed similar reductions in A1c at the 24-week endpoint [last observation carried forward (LOCF), ≥ 65 years: least squares mean

| Table 1 Baseline demographics and patient characteristics |
|-----------------|-----------------|-----------------|-----------------|
| Variable        | ≥ 65 years (N = 214) | < 65 years (N = 542) | p value         |
| Age, years      | 70.42 (4.35)     | 54.25 (7.77)     | < 0.001         |
| Age, LY IGlar/SA IGlar, years (%) | 29.8/26.8 | 70.2/73.2 | 0.376 |
| Sex, male, n (%) | 103 (48.1)      | 275 (50.7)       | 0.572           |
| Race, n (%)     |                  |                  |                 |
| American Indian or Alaska Native | 2 (0.9) | 36 (6.6) | < 0.001 |
| Asian           | 14 (6.5)         | 50 (9.2)         |                 |
| Black or African American | 9 (4.2) | 49 (9.0) |          |
| Multiple        | 0 (0.0)          | 3 (0.6)          |                 |
| White           | 189 (88.3)       | 404 (74.5)       |                 |
| Duration of diabetes, years | 14.42 (7.42) | 10.28 (6.17) | < 0.001         |
| Weight, kg      | 85.95 (18.60)    | 91.72 (19.80)    | < 0.001         |
| BMI, kg/m²      | 30.70 (5.35)     | 32.37 (5.44)     | < 0.001         |
| Glycated hemoglobin (%) | 8.06 (0.99) | 8.43 (1.09) | < 0.001         |
| Sulfonylurea use (yes), n (%) | 183 (85.5) | 447 (82.5) | 0.332          |
| Time of basal insulin injection [AM/(PM or bedtime)], % | 47.2/52.8 | 50.6/49.4 | 0.420          |
| Renal function status, n (%) |                  |                  | < 0.001         |
| Normal GFR (> 90 mL/min/1.73 m²) | 70 (32.7) | 440 (81.2) |          |
| Mild reduction in GFR (60–89 mL/min/1.73 m²) | 112 (52.3) | 88 (16.2) | |
| Moderate reduction in GFR (30–59 mL/min/1.73 m²) | 31 (14.5) | 13 (2.4) |          |
| Basal insulin ( ), SA IGlar/none | 45.3/54.7 | 37.3/62.7 | 0.047 |

Data are mean (SD) unless otherwise indicated
BMI body mass index, GFR glomerular filtration rate, LYIGlar LY2963016 insulin glargine, N total number of patients, SA IGlar insulin glargine, SD standard deviation

△ Adis
(LSM) ± standard error [SE] LY IGlar: −5.6 ± 2.2%, SA IGlar: −5.6 ± 2.2%, p = 0.814; <65 years: LY IGlar: −5.6 ± 2.2%; SA IGlar: −5.7 ± 2.2%, p = 0.262) (Fig. 1). No statistically significant age subgroup difference was observed for A1c (p = 0.700). The percentage of patients achieving their glycemic targets (A1c < 7%) was similar for both LY IGlar- and SA IGlar-treated patients in patients aged ≥ 65 years [LY IGlar: 55 (50.0%), SA IGlar: 55 (53.9%), p = 0.569] and in those aged < 65 years [LY IGlar: 125 (48.3%), SA IGlar: 142 (52.0%), p = 0.387].

Patients ≥ 65 years who were treated with LY IGlar or SA IGlar showed similar decreases in daily mean blood glucose (LSM ± SE, LY IGlar: −2.074 ± 0.25 mmol/L, SA IGlar: −1.919 ± 0.26 mmol/L, p = 0.617). Similar findings were observed in patients aged < 65 years (LY IGlar: −2.250 ± 0.19 mmol/L, SA IGlar: −2.382 ± 0.19 mmol/L, p = 0.487). There was no statistically significant effect of age for daily mean blood glucose (p = 0.086). No treatment differences between LY IGlar and SA IGlar were observed for FBG by SMBG in either age subgroup (Fig. 2).

Similar increases in basal insulin dose were observed in LY IGlar- and SA IGlar-treated patients across both age subgroups (Fig. 3). Basal insulin dose increased in both age subgroups at the 24-week endpoint (LOCF); however, the increase was significantly smaller in patients ≥ 65 years old (age group p < 0.001). Both treatment groups showed similar increases in body weight in patients ≥ 65 years old (LY IGlar: 1.412 ± 0.372 kg, SA IGlar: 1.397 ± 0.382 kg, p = 0.975) and < 65 years old (LY IGlar: 1.978 ± 0.281 kg, SA IGlar: 2.298 ± 0.279 kg, p = 0.282). However, patients aged ≥ 65 years exhibited statistically significantly smaller increases in body weight than patients under 65 years at the 24-week endpoint (LOCF) (age group p = 0.012).

Safety

The incidence and 1-year adjusted rates of total, documented symptomatic, and nocturnal hypoglycemia were similar for both LY IGlar and SA IGlar, regardless of age subgroup (Fig. 4). Too few patients (<10) experienced severe hypoglycemia for valid statistical analysis as prespecified in the Statistical Analysis Plan (LY IGlar: 3 patients; SA IGlar: 2 patients).

The overall proportion of patients with TEAR was similar in both treatment groups regardless of age subgroup [≥ 65 years, LY IGlar: 3 (2.8%), SA IGlar: 1 (1.0%), p = 0.363; < 65 years, LY IGlar: 11 (4.3%), SA IGlar: 13 (4.9%), p = 0.747]. Median insulin antibody levels (percent...
binding) were similar for LY IGlar- and SA IGlar-treated patients in both age subgroups (Table 2). Likewise, both treatment groups in each age subgroup showed similar incidences of AEs and SAEs (Table 3). Two patients (1 LY IGlar, 68 years and 1 SA IGlar, 67 years) died during the study. Neither death was considered by the investigator to be related to study drug.

**Treatment Between Age and Clinical Outcomes**

The change from baseline to endpoint (LOCF) for the clinical efficacy (Figs. 1–3 and p > 0.05 for weight) and safety (Fig. 4 and Tables 2 and 3) outcome measures was similar for each treatment group regardless of age. No statistically
significant treatment-by-age interaction was observed for patients in either age subgroup.

### DISCUSSION

The results of these subgroup analyses demonstrate similar clinical efficacy and safety outcomes within each age group for patients who receive LY IGlar or SA IGlar. Moreover, no effect of age was observed for any of the clinical efficacy and safety outcomes, except for basal insulin dose and body weight change. Older patients (≥ 65 years) required a lower basal insulin dose and gained less weight than younger patients (< 65 years). The effects of age on insulin dose and weight are consistent with previous reports of randomized controlled studies that evaluated insulin glargine in older (≥ 65 years) and younger (< 65 years) adults with T2D [9, 10].

This subgroup analysis of elderly patients (≥ 65 years) enrolled in the double-blind, phase 3 study showed similar hypoglycemic rates to patients under 65 years, which are consistent with hypoglycemia results seen in other studies comparing insulin glargine and NPH in older adults with T2D [9, 10]. In our subgroup analysis of elderly patients (≥ 65 years) enrolled in the double-blind, phase 3 study showed similar hypoglycemic rates to patients under 65 years, which are consistent with hypoglycemia results seen in other studies comparing insulin glargine and NPH in older adults with T2D [9, 10]. In our subgroup
Table 2 Insulin antibodies in patients

|                  | ≥ 65 years | p value | < 65 years | p value |
|------------------|------------|---------|------------|---------|
|                  | LY IGlar   | SA IGlar| LY IGlar   | SA IGlar|
|                  | N          | n (%)   | N          | n (%)   |
| Proportion of patients with detectable antibodies |            |         |            |         |
| Baseline         | 107        | 5 (4.7) | 97         | 1 (1.0) | 0.215  | 258    | 15 (5.8) | 268     | 12 (4.5) | 0.556  |
| 24-week endpoint (LOCF) | 107        | 3 (2.8) | 97         | 3 (3.1) | > 0.999 | 258    | 27 (10.5) | 268     | 19 (7.1) | 0.217  |
| Overall          | 107        | 12 (11.2)| 97         | 4 (4.1) | 0.071  | 258    | 44 (17.1) | 268     | 36 (13.4) | 0.275  |

|                  | N          | Median (Q1, Q3) | p value | N          | Median (Q1, Q3) | p value | N          | Median (Q1, Q3) | p value |
| Endpoint median insulin antibody levels |            |                 |         |            |                 |         |            |                 |         |
| Baseline         | 5          | 2.32 (0.44–2.97) | > 0.999 | 15         | 0.71 (0.46–1.54) | 0.251  | 12         | 0.44 (0.34–0.78) | 0.251  |
| 24-week endpoint (LOCF) | 3          | 1.96 (1.11–5.66) | 0.383  | 27         | 0.99 (0.38–5.14) | 0.616  | 19         | 0.65 (0.36–2.76) | 0.616  |

Values for N included in the analysis comprised only patients with detected or non-detected insulin antibody levels at baseline and post-baseline.

The unit of measurement for insulin antibodies is percent binding.

IQR interquartile range, LOCF last observation carried forward, LY IGlar LY2963016 insulin glargine, Q1 25th percentile, Q3 75th percentile, SA IGlar insulin glargine.

Overall refers to measurements taken during the 24-week treatment period and not at any specific visit or at endpoint (LOCF).
analysis, 2 patients (1 LY IGlar, 1 SA IGlar) ≥ 65 years and 3 patients (2 LY IGlar, 1 SA IGlar) < 65 years reported severe hypoglycemic events.

The risk of hypoglycemia is an important consideration when treating older adults with T2D. Older adults may not recognize the signs of hypoglycemia, particularly if they have cognitive deficits or comorbid diseases that make self-monitoring of glucose challenging [5, 8, 19, 20]. In addition, with hypoglycemic events, there is an additional concern of related complications, such as injuries from falls [21]. Treatment guidelines recommend a glycemic-improving medicine with a lower risk of hypoglycemia for older patients at moderate risk of hypoglycemia [5]. Therefore, insulin glargine may be a useful treatment option in older patients because of its lower risk of hypoglycemia vs other comparators (e.g., NPH) [8–10, 19]. Combining insulin glargine with OAM, such as metformin or glimepiride, compared with premixed insulins has been effective in reducing A1c with a lower risk of hypoglycemia when OAMs are no longer effective in achieving glycemic targets [22].

In our subgroup analysis, AEs in the LY IGlar and SA IGlar groups were similar. Four LY IGlar patients ≥ 65 years reported injection site reactions (Table 3), which were characterized by rash or redness, or pain at the injection site, and were mild to moderate in severity, and the patients recovered from the event. One SA IGlar patient ≥ 65 years reported an injection site reaction, which was severe in intensity, but not characterized by rash or redness at the injection site and the patient recovered from the event.

Elderly patients with diabetes often have more comorbidities [2]; however, patients with significant cardiac disease and active cancers were excluded from our study. Therefore, the older age (≥ 65 years) subgroup including 34 (15.9%) patients (≥ 75 years) may have been more representative of an older population that has fewer comorbid health problems. Considering this study’s limitation, it is important to remember, as experts and professional organizations recommend, that health care providers need to customize treatment on the basis of a patient’s lifestyle, health status, risk factors, cognitive function, medical history, and social support [2, 4, 5].

CONCLUSIONS

Our results demonstrate that LY IGlar and SA IGlar exhibit similar efficacy and safety in patients with T2D who are aged ≥ 65 years and in those who are aged < 65 years. For adult patients with T2D who require basal insulin as part of their treatment regimen, LY IGlar is an alternative basal insulin glargine that may be used with the same dose titration as SA IGlar.

Table 3  Adverse events summary for patients ≥ 65 and < 65 years

| Adverse events, n (%) | ≥ 65 years | p value | < 65 years | p value | Treatment-by-age subgroup interaction |
|----------------------|------------|---------|------------|---------|--------------------------------------|
|                      | LY IGlar   | SA IGlar| LY IGlar   | SA IGlar|                                      |
|                      | N = 112    | N = 102 | N = 264    | N = 278 |                                      |
| Patients with ≥ 1 TEAE | 63 (56.3)  | 56 (54.9)| 133 (50.4) | 128 (46.0)| 0.843  0.313  0.714               |
| Special topic assessmenta | 5 (4.5)  | 7 (6.9)  | 16 (6.1)  | 20 (7.2)| 0.447  0.597  0.695               |
| Injection site reactions | 4 (3.6)  | 1 (1.0)  | 9 (3.4)   | 8 (2.9)| 0.211  0.723  0.337               |
| Patients with ≥ 1 SAE | 8 (7.1)   | 11 (10.8)| 7 (2.7)   | 7 (2.5)| 0.351  0.922  0.487               |

*INT interaction, LY IGlar LY2963016 insulin glargine, N number of evaluable patients, n number of patients with TEAE, SAE serious adverse event, SA IGlar insulin glargine, TEAE treatment-emergent adverse event

a Categories of adverse events also include special topic assessment of adverse (allergic) events, injection site reactions, and SAEs though overall events are less than 5%
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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Declaration of Helsinki, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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

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