Has Basaglar® (insulin glargine) been studied in patients with type 1 diabetes?

SUMMARY

- ELEMENT 1 was a phase 3, randomized, multicenter, open-label, 52-week study that assessed the efficacy and safety of Basaglar compared with Lantus in the treatment of patients with type 1 diabetes on basal-bolus insulin therapy.[1]
- The LSM change in HbA1c levels from baseline to the 24-week primary endpoint was similar between treatment groups, thus demonstrating noninferiority of Basaglar treatment compared with Lantus treatment.[1]
- Both treatment groups demonstrated significant improvement in HbA1c levels from baseline to week 52 ($p<.001$). The percentage of patients who achieved HbA1c target levels ≤6.5% and <7% was similar between treatment groups.[1]
- Safety outcomes, such as the incidence and rate of hypoglycemia, change in body weight, and overall incidence of adverse events and insulin antibodies, were similar between treatment groups.[1]

CLINICAL STUDY IN PATIENTS WITH TYPE 1 DIABETES: ELEMENT 1

ELEMENT 1 was a phase 3, prospective, multinational, multicenter, randomized, open-label, 2-treatment group, parallel, 52-week study in patients with type 1 diabetes on basal-bolus insulin therapy.[1]

The study enrolled patients with type 1 diabetes who

- presented with a glycated hemoglobin (HbA1c) level ≤11% at screening
- had received basal-bolus insulin therapy ≥1 year, and
- had received once-daily basal insulin as NPH, Lantus® (insulin glargine) 100 units/mL, or detemir for ≥3 months along with mealtime regular human insulin, insulin lispro, aspart, or glulisine.[1]

Patients who were prior Lantus users were excluded if their regimen included twice-daily Lantus within 6 months of study entry. Patients with excessive resistance to insulin, defined as total daily insulin dose ≥1.5 units/kg, were also excluded.[1]

The open-label study design allowed for the use of a prefilled pen device, the planned insulin presentation for Basaglar® (insulin glargine) 100 units/mL, without the need to subject patients to additional injections.[1]

Study Objectives

The primary objective of the study was to determine that once-daily Basaglar was noninferior to once-daily Lantus, both in combination with preprandial insulin lispro administered 3 times a day, as assessed by change in HbA1c from baseline to the 24-week primary endpoint.[1]

The secondary objectives of the study were to compare Basaglar treatment with Lantus treatment, in combination with premeal insulin lispro, regarding

- noninferiority of Lantus treatment with Basaglar treatment as measured by change in HbA1c from baseline to 24 weeks
- HbA1c levels at 6, 12, 24, 36, and 52 weeks
- percentage of patients with HbA1c levels ≤6.5% and <7% at 24 and 52 weeks
- basal and prandial insulin doses at 24 and 52 weeks
- 7-point self-monitored blood glucose (SMBG) profiles at 24 and 52 weeks
- incidence and rate of hypoglycemia at 24 and 52 weeks
- body weight at 24 and 52 weeks
- incidence of adverse events during the study, and
- incidence of anti-insulin antibodies at 24 and 52 weeks.[1]

A subsequent evaluation was performed to assess for potential effects of insulin antibodies on select clinical outcomes.[2]

Study Design

The study design included a

- screening
- 24-week treatment period
- 28-week extension period, and
- 4-week posttreatment follow-up period (Figure 1).[1,3]

Figure 1. Design of the ELEMENT 1 Study[3]

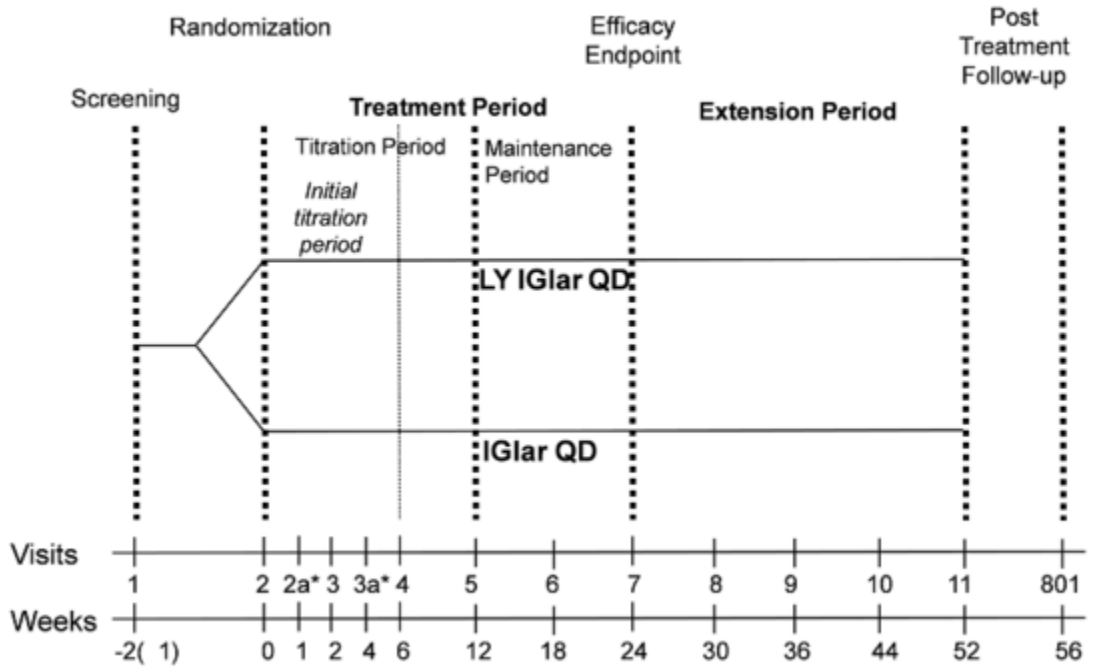

Figure 1 description: The design of the ELEMENT 1 study included a screening, a 24-week treatment period that was equally divided between titration and maintenance periods, a 28-week extension period, and a 4-week posttreatment follow-up period.

Abbreviations: IGlar = Lantus® (insulin glargine) 100 units/mL; LY IGlar = Basaglar® (insulin glargine) 100 units/mL; QD = once-daily administration.
* Telephone visits.

Basaglar and Lantus treatments were initiated at the same dose and at the same time of day as the patient's prestudy basal insulin.[1]

Insulin lispro was administered with meals at the same dose as the patient's prestudy mealtime insulin.[1]

Insulin doses were adjusted to minimize or avoid hypoglycemia while pursuing glycemic targets that included

- an HbA1c level <7%
- a fasting plasma glucose concentration ≤108 mg/dL, and
- a preprandial capillary blood glucose concentration between 70 to 130 mg/dL.[1]

Insulin doses were adjusted between week 0 and week 12 with subsequent dose changes directed by safety issues such as hypoglycemia.[1]

Patient Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar between treatment groups except for significantly more patients presenting with an HbA1c level <7% in the Basaglar treatment group compared with the Lantus treatment group (p<.05) (Table 1).[1]

Table 1. Patient Demographics and Baseline Characteristics in the ELEMENT 1 Study[1]

Assessment[a]	**Basaglar (n=268)**	**Lantus (n=267)**
Age, y	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, y	16 (11)	17 (11)
HbA1c, %	7.75 (1.13)	7.79 (1.03)
HbA1c group, n (%)		
<7.0%	73 (27)[b]	49 (18)
<8.5%	190 (71)	186 (70)
FPG by SMBG, mg/dL	151 (54)	147 (54)
Basal insulin (Lantus), n (%)	218 (81)	234 (88)
Insulin dose, units/d		
Basal	25.1 (12.9)	23.3 (11.6)
Prandial	30.5 (16.7)	29.5 (16.7)
Percent insulin antibody binding, median	0.69	0.88

Abbreviations: Basaglar = Basaglar® (insulin glargine) 100 units/mL; BMI = body mass index; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; Lantus = Lantus® (insulin glargine) 100 units/mL; SMBG = self-monitored blood glucose.

[a] Data presented as mean (SD) unless otherwise indicated.

[b] p<.05 vs Lantus.

Efficacy Outcomes

The least squares mean (LSM) change in HbA1c from baseline to week 24, as assessed by last observation carried forward (LOCF), was similar between treatment groups, thus demonstrating noninferiority of Basaglar treatment compared with Lantus treatment and of Lantus treatment compared with Basaglar treatment. Both treatment groups demonstrated significant improvement in HbA1c from baseline to week 52 (p<.001) (Table 2).[1]

The LSM HbA1c levels were similar between treatment groups at 6, 24, 36, and 52 weeks; however, at 12 weeks, patients treated with Basaglar were noted with a significantly higher LSM HbA1c level compared with those treated with Lantus (7.42% vs 7.31%; p=.03).[1]

There was no significant difference between treatment groups at 24 and 52 weeks (LOCF) in the

- percentage of patients who achieved HbA1c target levels ≤6.5% and <7%, and
- LSM daily basal and prandial insulin doses (Table 2).[1]

The LSM 7-point SMBG concentrations were similar between treatment groups at 24 and 52 weeks (LOCF) except for significantly lower LSM SMBG concentrations at bedtime at 24 and 52 weeks and at 3 AM at 24 weeks for patients treated with Basaglar compared with those treated with Lantus (p<.05).[1]

Table 2. Efficacy Outcomes in the ELEMENT 1 Study[1]

Assessment[a]	**Basaglar (n=268)**	**Lantus (n=267)**	**Basaglar (n=268)**	**Lantus (n=267)**
	24 Weeks		**52 Weeks**	
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 difference (95% CI)	0.108 (-0.002 to 0.219)		0.020 (-0.099 to 0.140)	
HbA1c, n (%)				
≤6.5%	54 (20)	49 (18)	42 (16)	36 (14)
<7%	92 (35)	86 (32)	81 (30)	67 (25)
FPG by SMBG, mg/dL	144 (4)	141 (4)	145 (4)	149 (4)
Basal insulin dose, units/d	27.77 (0.97)	26.05 (0.99)	28.46 (1.07)	26.40 (1.09)
Prandial insulin dose, units/d	26.34 (1.35)	25.07 (1.36)	27.80 (1.33)	27.10 (1.34)

Abbreviations: Basaglar = Basaglar® (insulin glargine) 100 units/mL; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; Lantus = Lantus® (insulin glargine) 100 units/mL; LOCF = last observation carried forward; LSM = least squares mean; SMBG = self-monitored blood glucose.

[a] Data presented as LSM (SE) and from LOCF unless otherwise indicated.

Safety Outcomes

Hypoglycemia

The incidence and rate of hypoglycemia, including total, nocturnal, and severe, at 24 and 52 weeks were similar between treatment groups (Table 3).[1]

Table 3. Incidence and Rate of Hypoglycemia at 24 and 52 Weeks in the ELEMENT 1 Study[1]

Assessment	24 Weeks		52 Weeks	
	Basaglar (n=268)	Lantus (n=267)	Basaglar (n=268)	Lantus (n=267)
Incidence of hypoglycemia, %				
Total	94	95	96	97
Nocturnal	82	80	86	88
Severe	2	3	4	4
Rate of hypoglycemia, mean (SD)[a]				
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)

Abbreviations: Basaglar = Basaglar® (insulin glargine) 100 units/mL; Lantus = Lantus® (insulin glargine) 100 units/mL.

[a] Events/patient/y. Represents all events reported during the 24-week treatment and 52-week (treatment and extension) periods.

Body Weight

There was no significant difference between treatment groups in body weight at 24 and 52 weeks (LOCF) (Table 4).[1]

Table 4. Body Weight of Patients at 24 and 52 Weeks (LOCF) in the ELEMENT 1 Study[1]

Assessment[a]	Basaglar (n=268)	Lantus (n=267)	Basaglar (n=268)	Lantus (n=267)
	24 Weeks		52 Weeks	
Body weight, kg	74 (1)	73 (1)	74 (1)	73 (1)
Change at week 24, kg	+0.36	+0.12	NA	NA
Change at week 52, kg	NA	NA	+0.71	+0.36

Abbreviations: Basaglar = Basaglar® (insulin glargine) 100 units/mL; Lantus = Lantus® (insulin glargine) 100 units/mL; LOCF = last observation carried forward; LSM = least squares mean; NA = not applicable.

[a] Data presented as LSM or LSM (SE).

Adverse Events and Serious Adverse Events

There was no significant difference between treatment groups in the incidence of

- adverse events, defined as events that first occurred or worsened in severity after randomization
- serious adverse events, which included episodes of severe hypoglycemia, and
- discontinuations due to adverse events (Table 5).[1]

A single patient in the Lantus treatment group died during the study; however, the investigator did not consider the death to be related to study drug or protocol procedures (Table 5).[1]

Table 5. Adverse Events During the ELEMENT 1 Study[1]

Assessment[a]	**Basaglar (n=268)**	**Lantus (n=267)**
AE	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 of diabetes	21 (8)	16 (6)
Special topic assessment of allergic reactions	20 (8)	11 (4)
Dermatitis, pruritus, rash, other[b]	7 (3)	4 (2)
Arthralgia, arthritis	4 (2)	5 (2)
Injection site[c]	6 (2)	2 (1)
Hypersensitivity	1 (<1)	1 (<1)
Allergic respiratory symptom, asthma	2 (1)	0 (0)
Injection site reaction[d]	7 (3)	3 (1)
Pain	6 (2)	2 (1)
Pruritus	2 (1)	1 (<1)
Rash	2 (1)	1 (<1)
SAE	20 (8)	24 (9)
Discontinuations due to an AE	2 (1)	6 (2)
Death	0 (0)	1 (<1)

Abbreviations: AE = adverse event; Basaglar = Basaglar® (insulin glargine) 100 units/mL; Lantus = Lantus® (insulin glargine) 100 units/mL; SAE = serious adverse event.

[a] Data presented as n (%). Treatment comparisons were not performed if there were <4 patients with events; patients may be counted in >1 category.

[b] Photosensitivity reaction, urticaria.

[c] Induration, nodule, reaction, swelling.

[d] Patient questionnaires.

Based on an incidence of ≥1% in either treatment group, there was no significant difference in the incidence of adverse events between treatment groups except for a higher incidence of dizziness reported in patients treated with Basaglar compared with those treated with Lantus (p=.03) (Table 6).[3]

Table 6. Adverse Events That Occurred in ≥1% in Either Treatment Group During the Treatment and Extension Periods in the ELEMENT 1 Study[3]

MedDRA Preferred Term[a]	Basaglar (n=268)	Lantus (n=267)
Nasopharyngitis	43 (16.0)	45 (16.9)
Upper respiratory tract infection	22 (8.2)	21 (7.9)
Hypoglycemia	13 (4.9)	12 (4.5)
Diarrhea	12 (4.5)	10 (3.7)
Back pain	10 (3.7)	9 (3.4)
Gastroenteritis	8 (3.0)	8 (3.0)
Sinusitis	7 (2.6)	8 (3.0)
Cough	6 (2.2)	8 (3.0)
Headache	7 (2.6)	7 (2.6)
Hypertension	9 (3.4)	5 (1.9)
Influenza	5 (1.9)	9 (3.4)
Bronchitis	4 (1.5)	8 (3.0)
Sinus congestion	6 (2.2)	5 (1.9)
Oropharyngeal pain	5 (1.9)	4 (1.5)
Urinary tract infection	4 (1.5)	5 (1.9)
Abdominal pain upper	3 (1.1)	5 (1.9)
Arthralgia	3 (1.1)	5 (1.9)
Gastroenteritis viral	5 (1.9)	3 (1.1)
Influenza-like illness	3 (1.1)	5 (1.9)
Vomiting	6 (2.2)	2 (0.7)
Fatigue	4 (1.5)	3 (1.1)
Gastritis	3 (1.1)	4 (1.5)
Gastroesophageal reflux disease	4 (1.5)	3 (1.1)
Musculoskeletal pain	2 (0.7)	5 (1.9)
Pharyngitis	3 (1.1)	4 (1.5)

MedDRA Preferred Term[a]	Basaglar (n=268)	Lantus (n=267)
Dizziness	6 (2.2)[b]	0 (0.0)
Nasal congestion	3 (1.1)	3 (1.1)
Upper respiratory tract inflammation	4 (1.5)	2 (0.7)
Acne	2 (0.7)	3 (1.1)
Depression	3 (1.1)	2 (0.7)
Dermatitis contact	1 (0.4)	4 (1.5)
Injection site reaction	3 (1.1)	2 (0.7)
Neck pain	2 (0.7)	3 (1.1)
Pain in extremity	3 (1.1)	2 (0.7)
Seasonal allergy	3 (1.1)	2 (0.7)
Tooth abscess	1 (0.4)	4 (1.5)
Toothache	4 (1.5)	1 (0.4)
Viral upper respiratory tract infection	3 (1.1)	2 (0.7)
Nausea	1 (0.4)	3 (1.1)
Pruritus	3 (1.1)	1 (0.4)
Pyrexia	4 (1.5)	0 (0.0)
Cystitis	0 (0.0)	3 (1.1)
Ligament sprain	3 (1.1)	0 (0.0)

Abbreviations: Basaglar = Basaglar® (insulin glargine) 100 units/mL; Lantus = Lantus® (insulin glargine) 100 units/mL; MedDRA = Medical Dictionary for Regulatory Activities.

[a] Data presented as n (%). Treatment comparisons were performed for events that occurred in >3 patients.

[b] p=.03 vs Lantus.

Antibodies

The number of patients with detectable antibodies and the median insulin antibody binding at 24 and 52 weeks were similar between treatment groups (Table 7).[1]

Table 7. Incidence of Detectable Antibodies and Percent Insulin Antibody Binding at 24 and 52 Weeks in the ELEMENT 1 Study[1]

Assessment	Basaglar (n=268)	Lantus (n=267)	Basaglar (n=268)	Lantus (n=267)
	24 Weeks		52 Weeks	
Incidence of detectable antibodies, n (%)[a]	80 (30)	90 (34)	107 (40)	105 (39)

Assessment	Basaglar (n=268)	Lantus (n=267)	Basaglar (n=268)	Lantus (n=267)
	24 Weeks		52 Weeks	
Percent insulin antibody binding, median[b]	1.17	1.10	0.92	0.89

Abbreviations: Basaglar = Basaglar® (insulin glargine) 100 units/mL; Lantus = Lantus® (insulin glargine) 100 units/mL; LOCF = last observation carried forward.

[a] Data represent overall 24- and 52-week study periods and not LOCF.

[b] Data represent LOCF.

The clinical outcomes of HbA1c, basal insulin dose in units/kg/day, and rate of total hypoglycemia as events/patient/30 days were not significantly affected by endpoint insulin antibody levels.[2]

A treatment-emergent antibody response (TEAR) was noted when patients

- who were insulin antibody-negative at baseline developed insulin antibody binding values ≥1.26% postbaseline, or
- with detectable insulin antibody levels at baseline presented with a ≥1% increase in insulin antibody binding and a ≥30% relative increase in insulin antibody binding from baseline.[2]

Over the 52-week study, there was no significant difference in TEAR between treatment groups. A TEAR occurred in

- 29 patients (10.9%) in the Basaglar treatment group, and
- 25 patients (9.4%) in the Lantus treatment group.[2]

There were no significant treatment-by-TEAR interactions for change in HbA1c, basal insulin dose, and total hypoglycemia rate from baseline to the 52-week endpoint (LOCF), indicating no significant differential treatment effect on these clinical outcomes for patients with or without TEAR.[2]

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Enclosed Prescribing Information

BASAGLAR® (insulin glargine) injection, for subcutaneous use, Lilly

HUMALOG® (insulin lispro injection), for subcutaneous or intravenous use, Lilly

References

The published references below are available by contacting 1-800-LillyRx (1-800-545-5979).

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(8):726-733. https://doi.org/10.1111/dom.12496

2. Ilag LL, Deeg MA, Costigan T, et al. Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus® insulin glargine in patients with type 1 or type 2 diabetes mellitus. *Diabetes Obes Metab*. 2016;18(2):159-168. http://dx.doi.org/10.1111/dom.12584

3. Data on file, Eli Lilly and Company and/or one of its subsidiaries.