Has Basaglar® (insulin glargine) been studied in patients with type 2 diabetes?

SUMMARY

- ELEMENT 2 was a phase 3, randomized, multicenter, double-blind, 24-week study that assessed the efficacy and safety of Basaglar compared with Lantus, both in combination with OAMs, in the treatment of patients with type 2 diabetes who were insulin naïve or received prior treatment with Lantus.[1]
- The LSM change in HbA1c levels from baseline to week 24 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 24 ($p<.001$). 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 2 DIABETES: ELEMENT 2

ELEMENT 2 was a phase 3, prospective, multinational, multicenter, randomized, double-blind, 2-treatment group, parallel, 24-week study in patients with type 2 diabetes who were insulin naïve or received prior treatment with Lantus® (insulin glargine) 100 units/mL.[1]

The study enrolled patients with type 2 diabetes who had received stable doses of ≥2 oral antihyperglycemic medications (OAMs) for 12 weeks and who

- were insulin-naïve and presented with a glycated hemoglobin (HbA1c) level ≥7.0% and ≤11.0%, or
- had received prior Lantus treatment and presented with an HbA1c level ≤11.0%.[1]

Patients were excluded from the study if they presented with a history of

- basal-bolus insulin therapy
- insulin therapy other than Lantus within 30 days of study entry, or
- excessive resistance to insulin, defined as a total daily insulin dose ≥1.5 units/kg.[1]

A double-blind design was possible due to the use of covered vials that concealed the differences between the Basaglar® (insulin glargine) 100 units/mL and Lantus vials.[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 OAMs, as assessed by change in HbA1c from baseline to 24 weeks.[1]

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

- noninferiority of Lantus treatment with Basaglar treatment as measured by change in HbA1c from baseline to 24 weeks
- HbA1c levels at 4, 8, 12, 16, 20, and 24 weeks
- percentage of patients with HbA1c levels ≤6.5% and <7% at 24 weeks
- insulin dose at 24 weeks
- 7-point self-monitored blood glucose (SMBG) profiles at 24 weeks
- incidence and rate of hypoglycemia at 24 weeks
- body weight at 24 weeks
- incidence of adverse events during the study, and
- incidence of anti-insulin antibodies at 24 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, and
- 4-week posttreatment follow-up period (Figure 1).[1,3]

Figure 1. Design of the ELEMENT 2 Study[3]

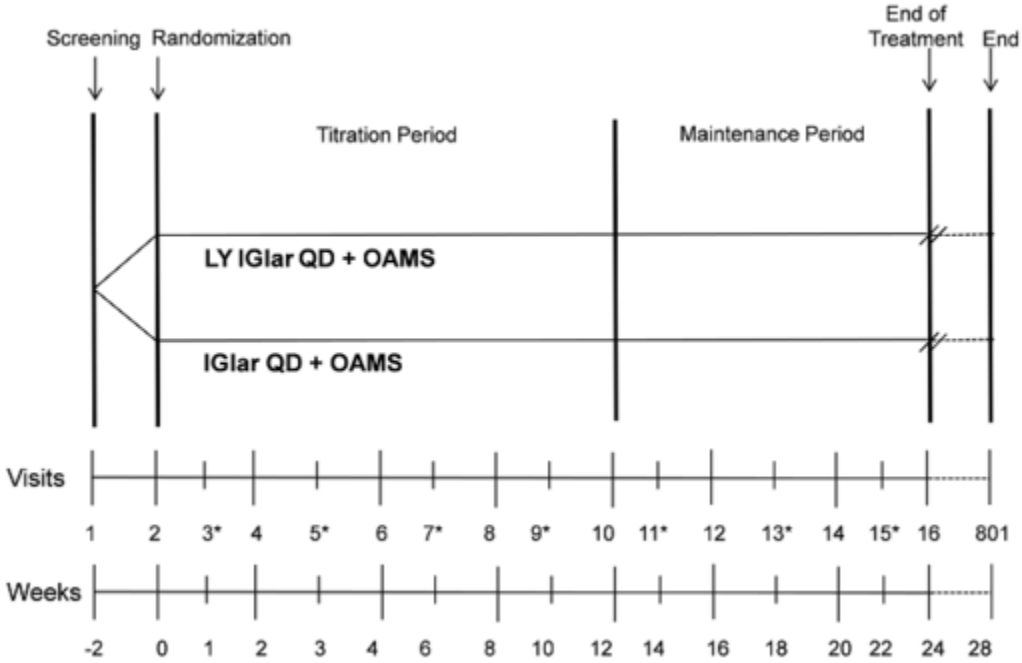

Figure 1 description: The design of the ELEMENT 2 study included a screening, a 24-week treatment period that was equally divided between titration and maintenance periods, and a 4-week posttreatment follow-up period.

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

Patients previously prescribed Lantus initiated Basaglar or Lantus at the prestudy Lantus dose.[1]

The initial dose of Basaglar and Lantus for insulin-naïve patients was 10 units once daily.[1]

As described by Gerstein et al,[4] patients followed a patient-driven titration schedule to increase their initial insulin dose by 1 unit daily until a fasting plasma glucose concentration of ≤100 mg/dL was achieved.[1]

In Korea and Taiwan, due to the availability of syringes only marked in 2-unit increments, patients followed a patient-driven titration schedule to increase their initial dose by 2 units every other day until a fasting blood glucose concentration of ≤100 mg/dL was achieved.[3]

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

Patients were to remain on their prestudy OAMs throughout the study.[1]

Patient Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar between treatment groups except for significantly fewer patients receiving 2 OAMs prior to randomization in the Basaglar treatment group compared with the Lantus treatment group (p=.046) (Table 1).[1]

Table 1. Patient Demographics and Baseline Characteristics in the ELEMENT 2 Study[1]

Assessment[a]	**Basaglar (n=376)**	**Lantus (n=380)**
Age, y	59 (10)	59 (10)
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)
BMI, kg/m^2	32 (6)	32 (5)
Duration of diabetes, y	12 (7)	11 (7)
HbA1c, %	8.34 (1.09)	8.31 (1.06)
HbA1c group, n (%)		
<7.0%	19 (5)	25 (7)
<8.5%	209 (56)	210 (55)
FPG by SMBG, mg/dL	159 (45)	160 (44)
Basal insulin (Lantus), n (%)	155 (41)	144 (38)
Time of basal insulin injection, n (%)		
Daytime	187 (50)	188 (50)
Evening or bedtime	189 (50)	192 (51)
Sulfonylurea use, n (%)	315 (84)	315 (83)
Treatment with 2 OAMs, n (%)[b]	298 (79.3)[c]	323 (85)

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; OAM = oral antihyperglycemic medication; SMBG = self-monitored blood glucose.

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

[b] Commonly used combinations included metformin and a sulfonylurea (62.4%) and metformin and dipeptidyl peptidase-4 inhibitors (10.1%).

[c] p=.046 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 24 (p<.001) (Table 2).[1]

The LSM HbA1c levels were similar between treatment groups at all assessed time points.[1]

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

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

The LSM 7-point SMBG concentrations were similar between treatment groups at 24 weeks (LOCF) except for a significantly lower LSM SMBG concentration at the midday premeal time point for patients treated with Basaglar compared with those treated with Lantus (122.58 vs 128.16 mg/dL; p=.04).[1]

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

Assessment[a]	**Basaglar (n=376)**	**Lantus (n=380)**
HbA1c, %		
Endpoint	7.04 (0.06)	6.99 (0.06)
Change from baseline	-1.29 (0.06)	-1.34 (0.06)
LSM difference (95% CI)	0.052 (-0.070 to 0.175)	
HbA1c group, n (%)		
≤6.5%	99 (27)	114 (30)
<7.0%	180 (49)	197 (53)
FPG by SMBG, mg/dL[b]	-48 (3)	-46 (3)
Insulin dose, units/kg/d	0.50 (0.03)	0.48 (0.03)

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.

[b] Represents change from baseline.

Safety Outcomes

Hypoglycemia

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

Table 3. Incidence and Rate of Hypoglycemia at 24 Weeks in the ELEMENT 2 Study[1]

Assessment	Basaglar (n=376)	Lantus (n=380)
Incidence of hypoglycemia, %		
Total	79	78
Nocturnal	57	54
Severe	<1	<1
Rate of hypoglycemia, mean (SD)[a]		
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)

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 period.

Body Weight

There was no significant difference between treatment groups in change in body weight at 24 weeks (LOCF). The LSM (SE) change in body weight was

- 1.8 (0.3) kg in patients treated with Basaglar, and
- 2.0 (0.3) kg in patients treated with Lantus.[1]

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 4).[1]

A single patient in each treatment group died during the study; however, the investigator did not consider the deaths to be related to study drug or protocol procedures (Table 4).[1]

Table 4. Adverse Events During the ELEMENT 2 Study[1]

Assessment[a]	Basaglar (n=376)	Lantus (n=380)
AE	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 of diabetes	19 (5)	18 (5)

Assessment[a]	Basaglar (n=376)	Lantus (n=380)
Special topic assessment of allergic reactions	21 (6)	27 (7)
Dermatitis, pruritus, rash, other[b]	8 (2)	12 (3)
Arthralgia, periarthritis	7 (2)	9 (2)
Injection site[c]	5 (1)	4 (1)
Asthma, nasal edema	3 (1)	5 (1)
Injection site reaction[d]	13 (4)	11 (3)
Pain	10 (3)	5 (1)
Pruritus	4 (1)	4 (1)
Rash	3 (1)	3 (1)
SAE	15 (4)	18 (5)
Discontinuations due to an AE	6 (2)	11 (3)
Death	1 (<1)	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 (%). Patients may be counted in >1 category.

[b] Angioedema, macular rash, papular rash, pruritic rash, or vesicular rash.

[c] Induration, pruritus, reaction.

[d] Based on patient questionnaires and treatment comparisons were not performed.

Based on an incidence of ≥1% in either treatment group, there was no significant difference in the incidence of adverse events between treatment groups (Table 5).[3]

Table 5. Adverse Events That Occurred in ≥1% in Either Treatment Group at 24 Weeks in the ELEMENT 2 Study[3]

MeDRA Preferred Term[a]	Basaglar (n=376)	Lantus (n=380)
Nasopharyngitis	21 (5.6)	22 (5.8)
Upper respiratory tract infection	19 (5.1)	15 (3.9)
Diarrhea	9 (2.4)	14 (3.7)
Back pain	9 (2.4)	10 (2.6)
Influenza	7 (1.9)	11 (2.9)
Cough	8 (2.1)	8 (2.1)
Nausea	8 (2.1)	8 (2.1)
Arthralgia	7 (1.9)	8 (2.1)
Headache	8 (2.1)	6 (1.6)

MeDRA Preferred Term[a]	Basaglar (n=376)	Lantus (n=380)
Urinary tract infection	7 (1.9)	7 (1.8)
Abnormal weight gain	10 (2.7)	3 (0.8)
Bronchitis	6 (1.6)	7 (1.8)
Gastroenteritis viral	7 (1.9)	6 (1.6)
Weight increased	5 (1.3)	7 (1.8)
Dizziness	6 (1.6)	5 (1.3)
Hypertension	8 (2.1)	3 (0.8)
Edema peripheral	5 (1.3)	6 (1.6)
Sinusitis	8 (2.1)	3 (0.8)
Vomiting	5 (1.3)	6 (1.6)
Oropharyngeal pain	6 (1.6)	4 (1.1)
Constipation	4 (1.1)	5 (1.3)
Pain in extremity	4 (1.1)	5 (1.3)
Sinus congestion	5 (1.3)	4 (1.1)
Hypoaesthesia	4 (1.1)	4 (1.1)
Pruritus	4 (1.1)	4 (1.1)
Abnormal loss of weight	4 (1.1)	3 (0.8)
Asthma	2 (0.5)	5 (1.3)
Dyspnea	3 (0.8)	4 (1.1)
Sinus headache	5 (1.3)	2 (0.5)
Gastroenteritis	2 (0.5)	4 (1.1)
Abdominal pain upper	1 (0.3)	4 (1.1)
Depression	1 (0.3)	4 (1.1)
Gastroesophageal reflux disease	1 (0.3)	4 (1.1)
Muscle spasms	4 (1.1)	1 (0.3)
Myalgia	1 (0.3)	4 (1.1)
Paraesthesia	0 (0.0)	4 (1.1)

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 (%).

Antibodies

The number of patients with detectable antibodies and the median insulin antibody binding at 24 weeks were similar between treatment groups (Table 6).[1]

Table 6. Incidence of Detectable Antibodies and Percent Insulin Antibody Binding at 24 Weeks in the ELEMENT 2 Study[1]

Assessment	Basaglar (n=376)	Lantus (n=380)
Incidence of detectable antibodies, n (%)[a]	56 (15)	40 (11)
Percent insulin antibody binding, median[b]	1.07	0.65

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-week treatment period 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 24-week study, there was no significant difference in TEAR between treatment groups. A TEAR occurred in 14 patients (3.8%) in each 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 24-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

REFERENCES

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

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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.

4. Gerstein HC, Yale JF, Harris SB, et al. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) study. *Diabet Med.* 2006;23(7):736-742. http://dx.doi.org/10.1111/j.1464-5491.2006.01881.x