Common Drug Review

Subsequent Entry Biologic Review Report

November 2016

Drug	Insulin glargine (rDNA origin) injection (Basaglar)
Indications	1. Treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. 2. Treatment of pediatric patients (> 6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.
Listing request	List in accordance to the Health Canada-approved indications
Dosage form(s)	Solution for injection 100 U/mL
NOC date	September 1, 2015
Manufacturer	Eli Lilly Canada

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in endocrinology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

A1C	glycated hemoglobin
ALBSS	Adult Low Blood Sugar Survey
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
BG	blood glucose
CAN	Consumer Advocare Network
CDA	Canadian Diabetes Association
CDR	CADTH Common Drug Review
CI	confidence interval
C_{max}	maximum plasma concentration
CMH	Cochran–Mantel–Haenszel
CSR	Clinical Study Report
CTD	Common Technical Document
DB	double-blind
FAS	full analysis set
FBG	fasting blood glucose
GIR	glucose infusion rate
G_{tot}	total glucose infusion over the clamp duration
ITSQ	Insulin Treatment Satisfaction Questionnaire
ITT	intention-to-treat
LOCF	last observation carried forward
LS	least squares
ODB	Ontario Drug Benefit
PD	pharmacodynamic
PK	pharmacokinetic
R_{Max}	maximum glucose infusion rate
SAE	serious adverse event
SE	standard error
SEB	subsequent entry biologic
SD	standard deviation
SMBG	self-monitoring of blood glucose
TEAE	treatment-emergent adverse event
TEAR	treatment-emergent antibody response
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing Basaglar followed the CDR Procedure and Submission Guidelines for Subsequent Entry Biologics. The CDR review team validated information provided by the manufacturer regarding product information (section 1), the indication under review (section 2), the rationale for the reimbursement criteria requested by the manufacturer (section 3), biosimilarity (section 4), extrapolation of indications (section 6), and the comparative cost of the new product (section 7). CDR reviewers provided a critical appraisal of the clinical evidence (section 5) and cost comparison (section 7).

Product Information

Basaglar (insulin glargine [rDNA origin] injection) is a subsequent entry biologic (SEB) based on the innovator Lantus. It has been approved in Canada for once-daily subcutaneous administration in the treatment of:

- Patients older than 17 years with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia
- Pediatric patients (older than six years) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Clinical Evidence

Six phase 1 studies and two phase 3 studies were the basis of the submission to Health Canada. One phase 1 study and two phase 3 studies were submitted to CDR for the purposes of this review.

ABEO was a phase 1 study of 91 healthy patients that compared the pharmacodynamics and pharmacokinetics of Basaglar with US-approved Lantus. Health Canada reviewed this study and in conjunction with its review of the other pharmacokinetic (PK)/pharmacodynamic (PD) studies, Health Canada reviewers concluded that Basaglar had similar PK/PD properties to both US Lantus and European Union (EU) Lantus. There was a predominance of Asian patients in the study (99%), but there is no strong reason to believe that the PD results of this bioequivalence study as observed in Asian patients would not also apply to non-Asian patients.

ELEMENT 1 was a randomized, multinational, open-label, non-inferiority study lasting 52 weeks of patients with type 1 diabetes mellitus. The primary outcome of the study was least squares (LS) mean change in glycated hemoglobin (A1C) from baseline to week 24. The difference in A1C between treatments from baseline to week 24 was 0.11% (95% CI, −0.005% to 0.217%; $P < 0.061$). Basal insulin dose was similar at week 24 in both treatment groups. Basaglar was found to be non-inferior to Lantus at the pre-specified 0.4% non-inferiority margin at this time point and also at the week 52 time point. There were no statistically significant differences in the incidence of adverse events (AEs) and serious adverse events (SAEs). Injection-site reactions occurred at similar rates in the Basaglar and Lantus groups. The overall and nocturnal hypoglycemia rates (events/person/year) were similar in the Basaglar and Lantus groups at weeks 24 and 52. The open-label design of ELEMENT 1 may have resulted in an imbalance in prognostic factors between the treatment groups as the trial progressed. This could have biased the results, but the direction of the bias is unknown.

ELEMENT 2 was a randomized, multinational, blinded, non-inferiority study of patients with type 2 diabetes mellitus. The primary outcome was change in A1C from baseline to week 24. The difference in A1C between treatments from baseline to week 24 was 0.052% (95% CI, −0.070% to 0.175%). Basaglar was found to be non-inferior to Lantus at the pre-specified 0.4% and 0.3% non-inferiority margins at week 24. Basal insulin dose was similar at week 24 in both treatment groups. Similar to the findings in ELEMENT 1, there were no statistically significant differences in the incidence of AEs and SAEs between the treatment groups. Injection-site reactions were rare and occurred at similar rates in the Basaglar and Lantus groups (~1%). The overall and nocturnal hypoglycemia rates (events/person/year) were similar in the Basaglar and Lantus groups at week 24.

While the patients in ELEMENT 1 and ELEMENT 2 were not all using Lantus prior to study entry, a significant proportion were using Lantus (84% in the type 1 diabetes mellitus study, 40% in the type 2 diabetes mellitus study). It would have been of interest to review the data for the subgroup of patients who switched from Lantus to Basaglar and to review the Basaglar dose changes over time in this subgroup. This information was not provided by the manufacturer.

Clinical Expert Comments

The clinical expert for this review noted that prescribers in Canada typically write the brand name of the product for insulin prescriptions (e.g., Lantus) rather than the generic name (insulin glargine). While this may affect uptake in the Canadian market, the clinical expert believed that there are negligible clinical concerns for switching patients from Lantus to Basaglar, and that this switch would be particularly advantageous in patients for whom cost is a significant issue. The clinical expert noted the absence of a vial dosage form for Basaglar, but did not think that this was a problem because vials are used far less commonly than pen-type devices.

Extrapolation

Health Canada allowed one extrapolation of the indication for the treatment of pediatric patients (older than six years) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. This was based on the similarity between Basaglar and Lantus "in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and based on clinical experience with the reference products."[1]

Cost Comparison

The manufacturer's submitted price for Basaglar ($0.0526 per unit of insulin) is 15% lower than the price of Lantus ($0.0619 per unit of insulin), when using the Ontario Drug Benefit (ODB) formulary list price for Lantus.

Conclusions

Basaglar has been approved in Canada for the treatment of patients with diabetes based on six phase 1 trials and two phase 3 clinical trials that demonstrated similar pharmacokinetics, pharmacodynamics, clinical efficacy, and harms compared with the innovator reference product, Lantus. At the manufacturer's submitted confidential price, Basaglar is 15% less expensive than Lantus based on the ODB price of Lantus.

1. PRODUCT INFORMATION

1.1 Overview of the Subsequent Entry Biologic Product

TABLE 1: SUBSEQUENT ENTRY BIOLOGIC OVERVIEW

Characteristics	Manufacturer-Provided Details	
	Subsequent Entry Biologic	Reference Product
Brand name	Basaglar	Lantus
Non-proprietary name	Insulin glargine (rDNA origin) injection	Insulin glargine (rDNA origin) injection
Manufacturer	Eli Lilly Canada	Sanofi
Strength(s)	100 units/mL	100 units/mL
Dosage form	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Drug Identification Number(s)	02444844 (cartridge) 02444852 (pre-filled pen)	02251930 (cartridge) 02294338 (pre-filled pen) 02245689 (10 mL vial)
Therapeutic classification	A10AE INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	A10AE INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING
Excipients	Glycerin, m-Cresol, zinc oxide and water for injection Hydrochloric acid and sodium hydroxide for pH adjustment	Glycerol 85%, m-Cresol, polysorbate 20 (10 mL vial only), zinc, and water for injection. Hydrochloric acid and sodium hydroxide for pH adjustment
Impurities[a]	[redacted]	—

[a] Includes both product and process-related impurities.

Basaglar (insulin glargine [rDNA origin]) injection is a recombinant human insulin analogue that is a long-acting, parenteral blood glucose–lowering drug.

1.1.1 Pharmaceutical Form and Composition

The primary amino acid sequence of Basaglar is the same as that of the active ingredient in Lantus. Both Basaglar and Lantus differ from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C terminus of the B chain. Structural testing and comparison with published data has demonstrated that Basaglar is highly similar to Lantus.[i]

1.1.2 Dosage Form, Strength, and Route of Administration

Basaglar and Lantus are intended for use as a subcutaneous injection. Basaglar will be available in two presentations:

- 100 units/mL solution for injection in a 3 mL cartridge for use with a reusable pen
- 100 units/mL solution for injection in a 3 mL pre-filled disposable pen (KwikPen).

Similarly, Lantus is also available in a 100 units/mL concentration as a 3 mL cartridge and a pre-filled pen (SoloSTAR) format; however, Lantus is also available in a third format: a 10 mL vial at the same concentration (100 units/mL) for use with a syringe.

1.1.3 Purity and Impurities

[redacted] (see Figure 1, Appendix 1: Additional Data). [redacted][ii].

[redacted] (see Figure 2, Appendix 1: Additional Data). [redacted][iii].

1.2 Overview of Lantus (Reference Product)

Lantus (insulin glargine injection [rDNA origin]) is a recombinant human insulin analogue that is a long-acting, parenteral blood glucose–lowering drug. It is indicated for once-daily subcutaneous administration in the treatment of patients older than 17 years with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. Lantus is also indicated in the treatment of pediatric patients (older than six years) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Lantus has been authorized for sale in Canada since 2002 and is currently actively marketed throughout Canada.

2. INDICATIONS

2.1 Health Canada–Approved Indications

Comparability between Basaglar and the reference product has been established based on comparative chemistry and manufacturing studies, comparative non-clinical studies, and comparative pharmacokinetic/pharmacodynamic (PK/PD) and clinical trials. Comparative PK/PD and clinical trials were carried out in healthy volunteers and in adult patients with type 1 or type 2 diabetes mellitus.

The indication for pediatric type 1 diabetes mellitus (age: older than six years) has been granted on the basis of similarity demonstrated between Basaglar and the reference product in product quality, mechanism of action, disease pathophysiology, safety profile, and dosage regimen, and based on clinical experience with the reference product.

Indication(s)	Extrapolation
Basaglar (insulin glargine [rDNA origin] injection) is a recombinant human insulin analogue indicated for once-daily subcutaneous administration in the treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.	No
Basaglar is also indicated in the treatment of pediatric patients (> 6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.	Yes

2.2 Proposed Indications Under Review by Health Canada

Proposed Indication(s)	Anticipated Date of NOC
No pending indications are currently under review by Health Canada	NA

NA = not applicable; NOC = Notice of Compliance.

3. MANUFACTURER'S REQUESTED LISTING CRITERIA

3.1 Requested Listing Criteria

TABLE 2: REQUESTED LISTING CRITERIA FOR INDICATIONS TO BE REVIEWED BY THE CADTH COMMON DRUG REVIEW

Requested Listing Criteria
The manufacturer requests that Basaglar be listed in accordance to the Health Canada–approved indications: • For once-daily subcutaneous administration in the treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia • In the treatment of pediatric patients (> 6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

3.2 Rationale for Requested Listing Criteria

Basaglar was approved as a subsequent entry biologic to Lantus by Health Canada on September 1, 2015.

- Data supporting Basaglar include six biopharmaceutical studies, two phase 3 clinical trials including one open-label study in type 1 diabetes and one double-blind study in type 2 diabetes patients, both with Lantus as the direct comparator.
- Predefined criteria used to establish similarity of PK and PD of Basaglar and Lantus were met in biopharmaceutical studies.
- In patients with type 1 diabetes mellitus also receiving prandial insulin, the control of glycated hemoglobin (A1C) levels with once-daily Basaglar is non-inferior to once-daily Lantus, and in secondary analysis, Lantus is non-inferior to Basaglar.
- In patients with type 2 diabetes mellitus also receiving oral antidiabetes medications, the control of A1C levels with once-daily Basaglar is non-inferior to once-daily Lantus, and in secondary analysis, Lantus is non-inferior to Basaglar.
- There are no clinically meaningful differences in rates of serious and treatment-emergent adverse events (TEAEs), rate of total, severe, or nocturnal hypoglycemic events, weight change, or immunogenicity with Basaglar or Lantus.
- Basaglar and Lantus were administered using similar dosing recommendations in the phase 3 clinical trials and, at study end point, there were no significant treatment differences in dose.
- The use of Basaglar in pediatric (older than six years) patients with type 1 diabetes mellitus is supported by the similar product quality characteristics of Basaglar and Lantus and by the similar pathophysiology of pediatric type 1 diabetes mellitus compared with the studied population (adult patients with type 1 diabetes mellitus).

4. BIOSIMILARITY

4.1 Quality Information

Extensive analytical comparisons were conducted and the US-approved and EU-approved Lantus products were found to be comparable to each other and to Basaglar. The comparative testing included structural characterization, batch release comparison, chromatographic profile, potency (biological activity) assay, impurity characterization, and stability assessment. The results are summarized in Table 3.

TABLE 3: COMPARATIVE TESTING RESULTS

Characteristic	Method	Result	Reference (CTDs)
Primary structure	N-terminal sequencing, intact mass and peptide mapping LC-MS	The primary sequence of the A and B chain were confirmed. Intact masses were all consistent with theoretical protein mass of 6,063.0 Da (≤ 0.007% mass difference).	Module 2.3 Comparative Assessment, pages 3 and 8
Secondary structure	Far-UV circular dichroism	Mean residue ellipticity in the far-UV region (195 nm to 260 nm) was similar, indicating the secondary structures are comparable.	Module 2.3 Comparative Assessment, pages 3 and 13
Secondary and tertiary structure	NMR — gHSQCAD	gHSQCAD spectra compared favourably, indicating the secondary and tertiary structures are comparable.	Module 2.3 Comparative Assessment, pages 3 and 13
Tertiary structure	Near-UV circular dichroism	Mean residue ellipticity in the near-UV region (250 nm to 350 nm) was similar, indicating the tertiary structure is comparable.	Module 2.3 Comparative Assessment, pages 3 and 13
Quaternary structure	Static light scattering	Apparent weight-average molecular weights are the same within the variability of the measurement.	Module 2.3 Comparative Assessment, pages 3 and 13
Batch release data	Comparison of each attribute to the release specifications	The testing results indicate that Basaglar Injection and the Lantus product are highly similar.	Module 2.3 Comparative Assessment, page 13
Chromatographic profile comparison	RP-HPLC and an orthogonal cation exchange	Overall, the chromatographic profiles are similar. [redacted]	Module 2.3 Comparative Assessment, pages 3 and 17
Biological potency comparison	The in vitro cell-based test. This is the same reporter gene method that is used for batch release	US- and EU-approved Lantus and Basaglar are comparable with respect to biological activity.	Module 2.3 Comparative Assessment, pages 4 and 20

Characteristic	Method	Result	Reference (CTDs)
Biological functionality assay	A panel of 8 biological functionality assays developed to measure insulin and IGF-1 receptor binding affinity, insulin receptor functional activity, and metabolic de novo lipogenesis activity, as well as mitogenic potential	Both the US- and EU-approved Lantus and Basaglar products were determined to be potent and functionally active insulin molecules. The results of the panel of binding assays support the conclusion that the products have equivalent biological activity.	Module 2.3 Comparative Assessment, pages 4 and 21
Stability data comparison	[redacted]	[redacted] Basaglar is similar to Lantus.	Module 2.3 Comparative Assessment, pages 4 and 21. Please see Module 2.3 Comparative Assessment, page 26, for detailed graphs on the HMWP comparison.

CTD = Common Technical Document; gHSQCAD = gradient heteronuclear single quantum coherence (adiabatic version); HMWP = high-molecular-weight protein; IGF = insulin-like growth factor; LC-MS = liquid chromatography–mass spectrometry; NMR = nuclear magnetic resonance; RP-HPLC = reversed-phase high-performance liquid chromatography; UV = ultraviolet.

4.2 Pivotal Clinical Studies

TABLE 4: PIVOTAL PHARMACOKINETIC/PHARMACODYNAMIC STUDY

Study Name	Design	Objectives	Population
ABE0[iv]	Randomized, double-blind, single dose (0.5 U/kg) 2-treatment, 4-period, crossover, replicate-treatment euglycemic clamp study	To evaluate the PK and PD similarity of Basaglar (test) and US Lantus (reference)	91 healthy adults

PD = pharmacodynamic; PK = pharmacokinetic.

TABLE 5: PIVOTAL PHASE 3 STUDIES

Study Name	Design	Objectives	Population
ELEMENT 1[v] (ABEB)	Prospective, randomized, multinational, parallel-arm, active-controlled, open-label study with a 24-week treatment period followed by 28-week extension period and 4 weeks of post-treatment follow-up	Primary efficacy outcome was non-inferiority of Basaglar to Lantus (EU- and US-approved) as measured by a change in A1C from baseline to end point when each is used in combination with prandial insulin lispro	536 adults with T1DM who were required to be on basal-bolus insulin therapy for at least 1 year prior to study entry
ELEMENT 2[vi] (ABEC)	Prospective, randomized, multinational, active-controlled, parallel group, double-blind study with a 24-week study period followed by 4 weeks of post-treatment follow-up	Comparison of Basaglar with Lantus (EU- and US-approved), as measured by change in A1C when each is used in combination with OADs	759 adults with T2DM who had either failed to achieve adequate glycemic control with at least 2 OADs and were insulin-naive, OR who were already taking Lantus in combination with at least 2 OADs

A1C = glycated hemoglobin; OAD = oral antidiabetes medication; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

4.2.1 Clinical Study 1: ABEO[vii]

(Clinical Study Report ABEO provided for full details.)

a) Study Characteristics

Study ABEO was a phase 1, randomized, double-blind, four-period, crossover, euglycemic clamp study conducted in 91 healthy patients (85 males, six females, aged 22 to 62 years) to evaluate the PK (primary objective) and PD similarity of Basaglar (test) and US-approved Lantus (reference).

TABLE 6: STUDY CHARACTERISTICS — ABEO

Characteristics		Details for ABEO
STUDY DESIGN	**Objective**	Pivotal PK/PD study to evaluate similarity of Basaglar and Lantus
	Blinding	Double-blind
	Study period	First patient entered (signed informed consent): September 20, 2012 Last patient completed: February 14, 2013
	Study centres	**Country (no. investigators)**: Singapore (1)
	Design	Single-site, randomized, double-blind, 2-treatment, 4-period, crossover, replicate-treatment, euglycemic clamp study in healthy patients
STUDY POPULATION	**Randomized (N)**	N = 91
	Inclusion criteria	• Overtly healthy men or women aged 21 to 65 years • BMI between 18.5 and 29.9 kg/m^2 • Fasting plasma glucose value < 108 mg/dL (6.0 mmol/L)
	Exclusion criteria	• Known allergies to insulin or its excipients • Major medical issues capable of altering the absorption, metabolism, or elimination or drugs, or of constituting a risk when taking study medication

Characteristics		Details for ABEO
DRUGS	**Intervention**	On 4 separate occasions, fasted patients received a single SC 0.5 U/kg dose of Basaglar or Lantus according to the following sequences: • Basaglar – Lantus – Basaglar – Lantus OR • Lantus – Basaglar – Lantus – Basaglar On day 1 of each of the 4 study periods, patients underwent a euglycemic clamp procedure. Patients were fasted and blood samples were collected during the 24-hour clamp procedure (–0.5, 0, 0.5, 2, 4, 6, 9, 12, 15, 18, 21 and 24 hours post-dose of each treatment period) for the PK analysis. Patients were discharged on day 2 of each period and there was a minimum washout period of 7 days between study periods.
	Comparator(s)	US Lantus
DURATION	**Run-in**	There was a 6-week screening period before the first clamp
	Treatment	Single injection of study drug + 24-hour euglycemic clamp procedure
	Follow-up	Patients were followed for 5 to 14 days after the fourth clamp procedure
OUTCOMES	**Primary end Point(s)**	To evaluate the PK similarity of Basaglar (test) to US-approved Lantus (reference) following SC administration of a single 0.5 U/kg dose to healthy patients
	Other end points	To demonstrate the PD similarity of Basaglar to US-approved Lantus following SC administration of a single 0.5 U/kg dose to healthy patients
NOTES	**Publications**	Linnebjerg H, Lam E, Segar M et al. Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and EU- and US-approved versions of Lantus insulin glargine in healthy patients: three randomized euglycemic clamp studies. Diabetes Care; 2015 Aug 25(online). The clinicaltrials.gov identification code: NCT: 01688635

BMI = body mass index; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous.

Intervention and Comparators

(Clinical Study Report [CSR], section 5.3 Study Design, p. 12–14)

The euglycemic clamp procedure aimed to maintain blood glucose at a target level (equivalent to 5 mg/dL (0.3 mmol/L) below the mean pre-dose fasting glucose) for approximately 24 hours after administration of Basaglar or US Lantus by infusing intravenous glucose. During the clamp, the glucose infusion rate (GIR) was varied to maintain the blood glucose concentration for each patient within approximately ± 5% of the target. In this way, the blood glucose concentrations were kept constant while the GIR varied, allowing the profile of GIR over time to be used as a measure of insulin action.

Outcomes

(CSR, section 7 Results, p. 21–31)

The primary PK outcomes were area under the curve from 0 to 24 hours (AUC[0-24]) and maximum plasma concentration (C_{max}). The primary PD outcomes were total glucose infusion over the clamp duration (G_{tot}) and maximum glucose infusion rate (R_{max}).

Statistical Analysis

Pharmacokinetic Statistical Analysis (Common Technical Document [CTD], Module 2.7.6 Synopses of Individual Studies, p. 14): The primary PK parameters, AUC(0-24) and C_{max}, were log-transformed prior to analysis. A linear mixed-effects model was fitted to the data. The model included patient as a random effect with period, sequence, and treatment as fixed effects. For each PK parameter, the difference in least squares (LS) means along with the 90% confidence intervals (CIs) were back-transformed to

produce the ratio of geometric means and the CI comparing Basaglar to Lantus. Similarity was to be concluded if the 90% CIs for both AUC(0-24) and C_{max} were contained within the interval of 0.80 to 1.25. The 0.80 to 1.25 range is the standard accepted margin for determining bioequivalence by most regulatory bodies including Health Canada.

Within- and between-patient variability were reported for each PK parameter. An analogous statistical analysis was performed for the log-transformed secondary PK parameters AUC(0-t_{last}) and AUC(0-∞). A nonparametric approach was taken to evaluate time to maximum plasma concentration (T_{max}) using the Wilcoxon signed-rank test. The difference in median T_{max} between treatments and the 95% CIs for the differences were presented.

An additional analysis was performed for the primary PK parameters, AUC(0-24) and C_{max}, as well as the secondary parameters, to include only the PK data obtained from patients who completed all four periods of the study and who had evaluable PK data in those periods. The model used for this analysis included period, sequence, treatment, and patient nested within-sequence as fixed effects; no random effects were included.

Pharmacodynamic Statistical Analysis (CTD, Module 2.7.6 Synopses of Individual Studies, p. 14): The primary PD parameters, R_{max} and G_{tot}, were log-transformed prior to analysis. A linear mixed-effects model was fitted to the data. The model included patient as a random effect with period, sequence, and treatment as fixed effects. For each PD parameter, the difference in LS means along with the 90% CIs were back-transformed to produce the ratio of geometric means and the CI comparing Basaglar to Lantus. Pharmacodynamic similarity was concluded if the 90% CI was contained within the interval of 0.80 to 1.25. The analysis was repeated using the same model with a corresponding 95% CI. Within- and between-patient variability were reported for each PD parameter. An additional analysis was performed for the primary PD parameters, G_{tot} and R_{max}, to include only the data obtained from patients who completed all four periods of the study. The model used for this analysis included period, sequence, treatment, and patient nested within-sequence as fixed effects; no random effects were included.

b) Results

Patient Disposition

(CSR for ABEO, section 6.2 Disposition, p. 19)

Ninety-one patients (85 males and six females) aged 22 to 62 years participated in the study comparing Basaglar with US-approved Lantus, with 82 patients completing the study. Three patients were withdrawn due to patient decision, two patients were withdrawn due to physician decision (inadequate venous access and noncompliance with study procedures, respectively), three patients were withdrawn due to dosing or glucose infusion errors, and one patient was withdrawn due to an AE of lethargy not considered by the investigator to be related to study treatment.

Efficacy Summary

(CSR, section 7 Results, p. 21–31)

Pharmacokinetic Evaluation: Based on statistical comparisons of AUC(0-24) and C_{max}, the primary PK parameters were demonstrated to be similar between Basaglar and Lantus. The ratios of LS geometric means were 0.90 and 0.92 for AUC (0-24) and C_{max}, respectively, with the 90% CIs for the ratios contained within the pre-specified interval of 0.80 to 1.25.

Mean (± standard deviation [SD]) serum C-peptide profiles for Basaglar and Lantus suggested a similar degree of suppression of the endogenous insulin following administration of Basaglar and Lantus.

Pharmacodynamic Evaluation: The statistical comparisons of G_{tot} and R_{max} demonstrated similarity in PD between Basaglar and Lantus. The ratios of LS geometric means were 0.91 and 0.93, respectively, for G_{tot} and R_{max}, with the 90% CIs for the ratios contained within the pre-specified interval of 0.80 to 1.25.

The results of this pivotal phase 1 study supported the Health Canada approval of Basaglar as a subsequent entry biologic (SEB) in Canada.

Safety Summary

(CSR for ABEO, section 8.1 to 8.3, p. 33)

No deaths or other serious adverse events (SAEs) occurred during this study. A total of [redacted] patients reported a total of [redacted] TEAEs, of which [redacted] TEAEs were considered to be unrelated to study treatment by the investigator. All reported TEAEs were mild ([redacted] AEs) or moderate ([redacted] AEs) in severity. [redacted] TEAE, an episode of [redacted] that was mild in severity, was considered to be related to study treatment. This AE occurred after dosing with 0.5 U/kg of Basaglar. Of the [redacted] TEAEs that were not considered by the investigator to be treatment-related, [redacted] TEAEs were considered by the investigator to be related to study procedures; the remaining non-treatment-related AEs were considered to be related to "other medical condition." The most common TEAEs (experienced by more than 10% of patients) were [redacted].

4.2.2 Clinical Study 2: ELEMENT 1 (ABEB)

a) Study Characteristics

ELEMENT 1 is a prospective, randomized, multinational, multi-centre, two-arm, active-controlled, open-label, parallel study. The study included a 24-week treatment period, a 28-week active-controlled extension period, and a four-week post-treatment follow-up. The primary objective of this study was to test the non-inferiority of Basaglar to Lantus as measured by change in A1C from baseline to 24 weeks, when used in combination with pre-meal insulin lispro in adult patients with type 1 diabetes.

TABLE 7: STUDY CHARACTERISTICS — ELEMENT 1

Characteristics		Details for ELEMENT 1 (ABEB)
STUDY DESIGN	**Objective**	Pivotal efficacy and safety study in adult patients with T1DM
	Blinding	Open-label
	Study period	September 8, 2011 (first patient enrolled) to August 13, 2012 (last patient completed)
	Study centres	**Country (no. investigators)**: Belgium (3), Germany (4), Greece (4), Hungary (5), Japan (8), Mexico (4), Poland (4), Romania (5), and the United States (22)
	Design	Prospective, randomized, multinational, multi-centre, two-arm, active-controlled, open-label, parallel-designed, non-inferiority study
STUDY POPULATION	**Randomized (N)**	N = 536
	Inclusion criteria	• Aged at least 18 years at screening • Diagnosis of T1DM based on WHO diagnostic criteria • Duration of diabetes of at least 1 year at screening • A1C of ≤ 11.0% • Basal-bolus insulin therapy for at least 1 year prior to screening • BMI of ≤ 35 kg/m^2

Characteristics		Details for ELEMENT 1 (ABEB)
	Exclusion criteria (list only major/select criteria)	• Prior exposure to a biosimilar insulin glargine • Excessive insulin resistance at study entry (total daily insulin dose ≥ 1.5 U/kg) • > 1 episode of severe hypoglycemia within 6 months of screening • Use of oral antidiabetes medications or received treatment with pramlintide or CSII in the 3 months prior to screening • Use of twice-daily insulin glargine in the 6 months prior to screening
DRUGS	**Intervention**	Patients were randomly allocated to once-daily Basaglar or once-daily Lantus administered subcutaneously, both in combination with pre-meal insulin lispro (at a dose that was equivalent to pre-study mealtime insulin). Pre-study basal insulin was converted on a unit-to-unit basis to either Lantus or Basaglar at randomization (for patients with adequate glycemic control) and was administered at the same time of day as pre-study basal insulin. Patients with suboptimal glycemic control at study entry had their insulin dose titrated as required to achieve adequate glycemic control.
	Comparator(s)	Once-daily subcutaneous Lantus (dose equivalent to pre-study basal insulin)
DURATION	**Run-in**	2 weeks (± 1 week)
	Treatment	24-week treatment followed by 28-week extension period
	Follow-up	4 weeks
OUTCOMES	**Primary end point(s)**	The pre-specified primary efficacy outcome was change in A1C from baseline to end point (week 24, or LOCF) based on the full analysis set. The primary treatment comparison was to compare Basaglar versus Lantus at the non-inferiority margin of 0.4%.
	Other end points	A key secondary treatment comparison was to compare Lantus insulin glargine versus Basaglar at the non-inferiority margin of –0.4%. Secondary efficacy outcomes included 7-point SMBG measurements, intra-patient variability (measured by SD of FBG), change in A1C from baseline to weeks 6 and 12 or week 24 (LOCF) or week 52 (LOCF), proportion of patients with A1C < 7% and ≤ 6.5%, basal and lispro dose at end of study (week 24 and week 52), and body weight. Pre-specified PRO measures included the ITSQ and the ALBSS. Safety outcomes included incidence of AEs including SAEs, allergic events, injection-site AEs, and hypoglycemic events. Insulin antibody levels were also assessed; specifically, the proportion of patients with detectable antibodies, and the number and proportion of patients who had a TEAR, defined as an absolute increase of ≥ 1% in insulin levels (measured by % binding) and ≥ 30% relative increase from baseline for patients who were insulin-antibody-positive at baseline, or changed from insulin-antibody-negative status at baseline to antibody-positive during the course of study.
NOTES	**Publications**	Blevins T.C., Dahl D., Rosenstock J., Ilag L.L., Huster W.J., Zielonka J.S., Pollom R.K., Prince M.J. Efficacy and safety of Basaglar insulin glargine compared with insulin glargine (Lantus) in patients with type 1 diabetes in a randomized controlled trial: The ELEMENT 1 study. Diabetes, Obesity and Metabolism. 2015Aug;17(8):726-733. • The clinicaltrials.gov identification code: NCT: 01421147

A1C = glycated hemoglobin; AE = adverse event; ALBSS = Adult Low Blood Sugar Survey; BMI = body mass index; CSII = continuous subcutaneous insulin infusion; FBG = fasting blood glucose; ITSQ = Insulin Treatment Satisfaction Questionnaire; LOCF = last observation carried forward; PRO = patient-reported outcome; SAE = serious adverse event; SD = standard deviation; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus; TEAR = treatment-emergent antibody response; WHO = World Health Organization.

Intervention and Comparators
Patients were randomly allocated to once-daily Basaglar or once-daily Lantus administered subcutaneously, both in combination with pre-meal insulin lispro (at a dose that was equivalent to pre-study mealtime insulin). Pre-study basal insulin was converted on a unit-to-unit basis to either Lantus or Basaglar at randomization (for patients with adequate glycemic control) and was administered at the same time of day as pre-study basal insulin. Patients with suboptimal glycemic control at study entry had their insulin dose titrated as required to achieve adequate glycemic control.

- EU- and US-approved Lantus were used in the trial.
- ELEMENT 1 was an open-label study.
- No concomitant medications were required or permitted during the study.

Outcomes
The primary efficacy outcome was change in A1C from baseline to end point (week 24, or last observation carried forward [LOCF]) based on the full analysis set (FAS). The primary treatment comparison was to compare Basaglar versus Lantus at the non-inferiority margin of 0.4%.

Key safety outcome measures included the incidence of AEs including SAEs, allergic events, injection-site AEs, and hypoglycemic events. Insulin antibody levels were also assessed; specifically, the proportion of patients with detectable antibodies, and the number and proportion of patients who had a treatment-emergent antibody response (TEAR), defined as an absolute increase of ≥ 1% in insulin levels (measured by % binding) and ≥ 30% relative increase from baseline for patients who were insulin-antibody-positive at baseline, or changed from insulin-antibody-negative status at baseline to antibody-positive during the course of study.

The Adult Low Blood Sugar Survey (ALBSS) was measured and contains 33 items, with each item scored on a five-point response scale: 0 (never) to 4 (almost always). Items are categorized in two domains: behaviour (or avoidance) items 1 to 15, and worry (or affect) items 16 to 33. Behaviour total score (TS) range is 0 to 60 and worry TS range is 0 to 72. Higher scores on behaviour items (related to avoidance of hypoglycemia) reflect greater awareness and/or effort of the participant to prevent low blood sugar. Higher scores on worry items (related to worries about low blood sugar and its consequences) reflect greater participant concern about having low blood sugar.[2]

The Insulin Treatment Satisfaction Questionnaire (ITSQ) was measured and is an instrument containing 22 items that assess treatment satisfaction for participants with diabetes and on insulin. Items are measured on a seven-point scale: 1 (no bother at all) to 7 (a tremendous bother), with lower scores reflecting better outcomes. Items are divided into five domains: inconvenience of regimen ([IR], five items: scores range from 5 to 35), lifestyle flexibility ([LF], three items: scores range from 3 to 21), glycemic control ([GC], three items: scores range from 3 to 21), hypoglycemic control ([HC], five items: scores range from 5 to 35), and insulin delivery device (IDD) (six items: scores range from 6 to 42). ITSQ total overall scores range from 22 to 154. Data presented are the transformed score on a scale of 0 to 100, where transformed score = 100 × [(7-raw score)/6]. Higher scores indicate better treatment satisfaction.[3]

Statistical Analyses
(CTD, Module 2.7.6 Synopses of Individual Studies, p. 43)
For Basaglar to show non-inferiority to Lantus at the 0.4% non-inferiority margin, a total of 368 completers at week 24 (184 in each treatment arm) were required. This calculation was based on the assumption that there would be no treatment difference in terms of A1C between Basaglar and Lantus

and a common SD of 0.884% for change from baseline in A1C, 0.05% two-sided significance level and over 99% power. Assuming that the dropout rate at week 24 was 15%, the required number of patients was 432 (216 per arm). An enrolment of 432 patients was required to show non-inferiority of Basaglar to Lantus at the 0.3% non-inferiority margin with 90% power.

- Significance testing of treatment effects and interactions between treatment groups were conducted at a two-sided alpha level of 0.05, with CIs calculated as two-sided 95% CIs, unless otherwise specified (no adjustments for multiplicity were performed).
- The non-inferiority margin of 0.4% was chosen because it is accepted by regulatory agencies and is widely used in diabetes clinical trials. Some regulatory guidelines also recommend testing at a non-inferiority margin of 0.3, which Basaglar also passed (following a gated approach).
- The primary analysis conducted was intention-to-treat.
- The primary analysis of change in A1C from baseline to week 24 was conducted using an analysis of covariance (ANCOVA) model. The model included country, time of basal insulin injection (daytime, evening/bedtime), and treatment as fixed effects and baseline A1C as a covariate. ANCOVA was also used for secondary analyses of ALBSS and ITSQ.
- If the upper limit of the 95% CI for the primary analysis was < 0.4%, then non-inferiority was concluded. If non-inferiority was met using the 0.4% margin, the comparison was made using the 0.3% margin. This gate-keeping procedure was used to control the type 1 error rate at a one-sided alpha of 0.025.

TABLE 8: SUMMARY OF STATISTICAL ANALYSES IN THE ELEMENT 1 TRIAL

Hypothesis Objective	Sample Size, Power Calculation	Data Management, Patient Withdrawals
Hypothesis: Basaglar once daily was non-inferior to Lantus insulin glargine once daily as measured by change in A1C from baseline to week 24 when used in combination with pre-meal insulin lispro.	To show non-inferiority at the 0.4% non-inferiority margin, 184 (368 total) completers per arm were required at 24 weeks, but assuming a 15% dropout rate at 24 weeks, the required number of randomized patients was 216 per arm (432 total). The same sample size was needed to show non-inferiority of Basaglar to Lantus at the 0.3% non-inferiority margin with 90% power.	Missing data were handled using the LOCF approach.

A1C = glycated hemoglobin; LOCF = last observation carried forward.

b) Results

Baseline Characteristics

TABLE 9: BASELINE PATIENT DEMOGRAPHICS AND PATIENT CHARACTERISTICS FOR THE ELEMENT 1 TRIAL

Baseline Characteristic	Basaglar n = 268	Lantus n = 267
Mean (SD) age (years)	41.0 (13.7)	41.4 (13.3)
Male, n (%)	155 (57.8)	155 (58.1)
Race, n (%)		
American Indian/Alaska Native	11 (4.1)	12 (4.5)
Asian	49 (18.4)	51 (19.1)
Black/African American	9 (3.4)	2 (0.7)
Multiple	1 (0.4)	1 (0.4)
White	197 (73.8)	201 (75.3)
Mean (SD) duration of diabetes (years)	16.2 (11.0)	16.6 (10.8)

Baseline Characteristic	Basaglar n = 268	Lantus n = 267
Mean (SD) A1C, %	7.8 (1.1)	7.8 (1.0)
A1C < 7%, n (%)	73 (27.2)	49 (18.4)
Time of basal injection, n (%)		
Daytime	51 (19.0)	48 (18.0)
Evening/bedtime	217 (81.0)	219 (82.0)

A1C = glycated hemoglobin; SD = standard deviation.

In ELEMENT 1, patient demographics and baseline characteristics were similar between treatment groups, with the exception of the proportion of patients with A1C < 7.0% at baseline. Overall, mean (SD) patient age was 41.0 (13.7) years and mean duration of type 1 diabetes was 16.4 years. Additionally, 58% patients were male and 75% patients were white. In the Basaglar group, there was a significantly higher proportion of patients with A1C < 7.0% at baseline (27.2%) than in the Lantus group (18.4%; *P* = 0.022). In terms of previous basal insulin use, 218 patients (81.3%) out of 268 in the Basaglar treatment group and 234 (87.6%) out of 267 in the Lantus group were taking Lantus at study entry (other types of basal insulin prior to study entry are not categorized).

Patient Disposition

A total of 536 patients were randomly allocated to treatment and one patient discontinued before receiving study drug; therefore, a total of 535 patients were included in the FAS population (268 in the Basaglar arm and 267 in the Lantus arm). A total of 245 patients in each arm completed the 52-week study.

TABLE 10: SUMMARY OF PATIENT DISPOSITION FOR ELEMENT 1 (ABEB)

Disposition	ELEMENT 1	
	Basaglar	Lantus
Screened, N	581	
Randomized, N	536	
At 24 weeks:		
Discontinued, N (%)	15 (5.6)	11 (4.1)
WDAEs, N (%)	2 (0.7)	3 (1.1)
Withdrawal due to SAEs, N (%)	1 (0.4)	2 (0.7)
Lost to follow-up, N (%)	1 (0.4)	1 (0.4)
At 52 weeks:		
Discontinued, N (%)	23 (8.6)	22 (8.2)
WDAEs, N (%)	2 (0.7)	6 (2.2)
Withdrawal due to SAEs, N (%)	1 (0.4)	5 (1.9)
Lost to follow-up, N (%)	2 (0.7)	2 (0.7)
Intention-to-treat, N	268	267
Per-protocol, N	245	245
Safety, N	268	267

SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Efficacy Results

A total of 535 patients were included in the FAS population (268 in the Basaglar arm and 267 in the Lantus arm, as one patient discontinued before receiving study drug). Basaglar and Lantus were associated with a significant decrease in A1C from baseline to week 24. The LS mean change in A1C from baseline to end point was −0.35% for the Basaglar group and −0.46% for the Lantus group, resulting in an LS mean difference (95% CI) between treatments from baseline to end point of 0.11% (−0.005 to 0.217%; $P < 0.061$). Per-protocol analyses of A1C are presented in Table 11. Basaglar was found to be non-inferior to Lantus at the 0.4% and 0.3% non-inferiority margins. Non-inferiority of Lantus to Basaglar was also demonstrated as a secondary end point and thus Basaglar and Lantus were consequently considered to have similar efficacy.

TABLE 11: SUMMARY OF A1C CHANGE IN ELEMENT 1 (PER-PROTOCOL)

		24-Week		52-Week	
	Baseline (BL)	End Point (EP) (LOCF) (%)	Δ BL to EP (LOCF) (%)	EP (LOCF) (%)	Δ BL to EP (LOCF) (%)
Basaglar					
n[a]	251	251	251	251	251
LS mean	7.752	7.390	–0.373[b]	7.484	–0.279[b]
Lantus					
n[a]	256	256	256	256	256
LS mean	7.774	7.291	–0.472[b]	7.479	–0.284[b]
LS mean diff (95% CI)			0.100 (–0.012 to 0.211)		0.005 (–0.117 to 0.127)

A1C = glycated hemoglobin; LOCF = last observation carried forward; LS = least squares.
[a] Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
[b] Within-treatment $P < 0.001$.
Source: Table 2.7.3.6 in Module 2.7.3 Summary of Clinical Efficacy.

In addition to the primary end point of change in A1C from baseline to week 24, change in A1C from baseline to the end of the 28-week extension period (week 52) was also included as a secondary end point. At the week 52 (LOCF) end point, the LS mean (standard error [SE]) change in A1C from baseline was −0.22% (0.80%) in the Basaglar group and −0.25% (0.75) in the Lantus group leading to a LS mean difference (95% CI) between treatments of 0.02% (−0.10 to 0.14%; $P = 0.737$). The treatment difference at week 52 met the non-inferiority margin of 0.4% and therefore Basaglar was shown to be non-inferior to Lantus.

The proportion of patients who achieved A1C targets of < 7.0% and ≤ 6.5% at end point (week 24) was similar between groups. In the Basaglar group, 34.5% of patients achieved A1C < 7.0%, with the corresponding figure in the Lantus group being 32.2%; the between-group difference was not statistically significant ($P = 0.335$). Similarly, 20.2% of Basaglar-treated patients and 18.4% of Lantus-treated patients achieved A1C levels of ≤ 6.5% at end point.

Analysis of seven-point self-monitoring of blood glucose (SMBG) profiles showed that LS mean blood glucose values were significantly lower at bedtime and at 3:00 a.m. in the Basaglar group than in the Lantus group. For the bedtime value, the decrease in blood glucose from baseline to end point was greater in the Basaglar group than in the Lantus group (LS mean difference [SE] at end point was

−0.48 mmol/L [0.23]; 95% CI, −0.94 to −0.03 mmol/L]; *P* = 0.038). For the 3:00 a.m. time point only the Basaglar-treated group showed a significant decrease in LS mean blood glucose measured from baseline to end point, with the between-treatment LS mean difference [SE] at end point being −0.45 mmol/L (0.21); 95% CI, −0.86 to −0.04 mmol/L; *P* = 0.033. There were no significant differences at any other time points.

Between baseline and end point, both treatment groups demonstrated similar increases in mean daily basal insulin dose, but there were no significant between-group differences in actual daily basal insulin dose or change in basal insulin dose from baseline to end point (Table 12). Additionally, both treatment groups had similar decreases in mean daily lispro doses from baseline to end point, but there were no significant between-group differences from baseline to end point.

TABLE 12: SUMMARY OF DAILY INSULIN DOSE CHANGE IN ELEMENT 1

	ELEMENT 1 (24-wk) N = 535		ELEMENT 1 (52-wk) N = 534	
	Basaglar N = 268	**Lantus N = 267**	**Basaglar N = 268**	**Lantus N = 267**
Basal Insulin Dose (U/day)				
No. of patients[a]	268	266	268	266
Mean baseline	25.1	23.3	25.1	23.3
LS mean change from baseline[b]	2.0	2.0	2.7	2.4
Total Insulin Dose (U/day)				
No. of patients[a]	264	266	264	266
Mean baseline[b]	55.5	52.8	55.5	52.8
LS mean change from baseline	0.7	0.6	2.9	2.9

LS = least squares.
[a] Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
[b] Change from baseline to end point values are LS means, reflecting adjustment for the design factors of the study. Baseline values are unadjusted means.
Source: Basaglar product monograph.

TABLE 13: SELECTED PATIENT-REPORTED OUTCOMES IN ELEMENT 1

	Basaglar (N = 268)	Lantus (N = 267)	Statistical Comparison
ALBSS Behaviour – 24 weeks (LOCF) (n = 255,257)	12.73 (0.66)	12.53 (0.66)	*P* = 0.778
ALBSS Worry – 24 weeks (LOCF) (n = 255,258)	15.39 (1.08)	14.27 (1.08)	*P* = 0.323
ITSQ Total – 24 weeks (LOCF) (n = 253,258)	74.46 (1.23)	74.23 (1.24)	*P* = 0.862

ALBSS = Adult Low Blood Sugar Survey; ITSQ = Insulin Treatment Satisfaction Questionnaire; LOCF = last observation carried forward; LS = least squares.
Note: Data are LS mean (standard error). LS mean are determined by analysis of covariance (ANCOVA) and adjusted for baseline A1C, country, time of basal insulin injection, and treatment.

Subgroup of Patients Who Switched From Lantus to Basaglar: In ELEMENT 1, 84% of the patients were already on Lantus. No statistically significant treatment differences were observed for the primary efficacy measure, change in A1C from baseline to the 24-week end point (LOCF), and 52-week end point (LOCF). No statistically significant treatment differences were observed for the proportions of patients achieving A1C targets at 52 weeks (LOCF). Increases in basal and prandial insulin doses (U/kg/day) from baseline to the 52-week end point (LOCF) were similar for both treatments. Daily mean blood glucose (BG) and fasting blood glucose (FBG) at 52 weeks were similar between both groups. A small, statistically significant treatment difference was observed for weight change where Basaglar-treated patients gained more weight with minimal LS mean per cent change from baseline (< 2%) (Basaglar: 1.81 ± 0.42; Lantus: 0.41 ± 0.39; *P* = 0.035).

A manuscript has been prepared by the manufacturer for publication that focuses on this subgroup of patients from both ELEMENT 1 and ELEMENT 2.[4]

Safety Results

One death, in the Lantus group, occurred during the 52-week study period. The patient experienced an SAE of hypertrophic cardiomyopathy with a fatal outcome, reported at visit 8 (week 30). The 48-year-old female was using Lantus prior to study entry, and had a medical history that included cardiomyopathy and hyperlipidemia. The event occurred approximately six months after initiating study drug and was not considered by the investigator to be related to study drug or study procedures.

During the 52-week study period, 62.8% (n = 167) patients in the Basaglar group had ≥ 1 TEAE and 7.5% (n = 20) had at least one SAE. The corresponding figures in the Lantus group were 62.2% (n = 166) and 9.0% (n = 24), respectively. TEAEs were similar in both treatment groups.

In the entire 52-week treatment period, a total of 515 (96.3%) patients reported 40,393 hypoglycemic events (including severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, or unspecified hypoglycemia). A total of 21 patients (3.9%) reported 29 severe hypoglycemic events over 52 weeks (in the Basaglar arm, 3.7% [n = 10] patients reported 13 severe events and in the Lantus arm, 4.1% [n = 11] patients reported 16 severe events). The between-arm difference in the incidence of severe hypoglycemic events from baseline to week 52 was not significant.

There were no statistically significant treatment differences in the overall proportion of patients with detectable insulin antibodies, the change in insulin antibodies (per cent binding) from baseline to 24- and 52-week end points (LOCF), or in the overall incidence of TEARs. Over the 52-week treatment period, 39.8% (n = 212) patients (Basaglar: 107 patients [40.4%]; Lantus: 105 patients [39.3%]; *P* = 0.859) had detectable antibodies to insulin. In addition, there were no significant treatment-by-TEAR interactions for any of the clinical outcomes tested (including change from baseline in A1C, rate of total hypoglycemia, and basal insulin dose), indicating no statistically significant differential treatment effect on these outcomes for patients with or without TEARs at the 52-week end point (LOCF).

4.2.3 Clinical Study 3: ELEMENT 2 (ABEC)

a) Study Characteristics

ELEMENT 2 is a prospective, randomized, multinational, multi-centre, two-arm, active-controlled, double-blind, parallel-designed study with a 24-week treatment period and a four-week post-treatment follow-up. The study compared two long-acting basal insulin analogues (Basaglar and Lantus) in patients with type 2 diabetes who were on two or more oral antidiabetes drugs and were either insulin-naive

with inadequate glycemic control or on Lantus with adequate or inadequate glycemic control. The primary objective of this study was to test the non-inferiority of Basaglar to Lantus as measured by change in A1C from baseline to 24 weeks, when used in combination with oral antidiabetes drugs in adult patients with type 2 diabetes.

TABLE 14: STUDY CHARACTERISTICS — ELEMENT 2

Characteristics		Details for ELEMENT 2 (ABEC)
STUDY DESIGN	**Objective**	Pivotal efficacy and safety study in adult patients with T2DM
	Blinding	Double-blind
	Study period	The first patient was enrolled and assigned to therapy on September 6, 2011. The last patient completed his/her week 24 visit on September 17, 2012.
	Study centres	**Countries (no. investigators):** Czech Republic (5), France (3), Germany (9), Greece (3), Hungary (7), Italy (3), Korea (5), Mexico (4), Poland (4), Puerto Rico (7), Spain (3), Taiwan (4) and the United States (31)
	Design	Prospective, randomized, multinational, multi-centre, two-arm, active-controlled, double-blind, parallel-designed, non-inferiority study
STUDY POPULATION	**Randomized (N)**	N = 759
	Inclusion criteria	• ≥ 18 years old at screening • Diagnosis of T2DM based on WHO diagnostic criteria • Receipt of ≥ 2 OADs at stable doses for 12 weeks prior to screening, with or without insulin glargine, in accordance with local product labels • A1C ≥ 7.0% and ≤ 11.0% if insulin-naive and A1C ≤ 11.0% if previously on insulin glargine • BMI ≤ 45 kg/m^2
	Exclusion criteria	• Use of any other insulin except insulin glargine in the previous 30 days • Exposure to a biosimilar insulin glargine in the previous 90 days • History of basal-bolus therapy, or requirement for mealtime insulin to achieve target glycemic control • Use of GLP-1 agonist in the previous 90 days • Use of pramlintide in the previous 90 days • Excessive insulin resistance (total insulin dose ≥ 1.5 U/kg) • > 1 episode of severe hypoglycemia in the previous 6 months
DRUGS	**Intervention and Comparator**	Basaglar administered subcutaneously once daily, in combination with OADs (n = 376) vs. Lantus administered subcutaneously once daily, in combination with OADs (n = 380)
DURATION	**Run-in**	2 weeks
	Treatment	24 weeks
	Follow-up	4 weeks
OUTCOMES	**Primary end point(s)**	The pre-specified primary efficacy outcome was change in A1C from baseline to end point (week 24 or LOCF). The primary treatment comparison was to compare Basaglar vs. Lantus at the non-inferiority margin of 0.4%.
	Other end points	A key secondary treatment comparison was to compare Lantus insulin glargine vs. Basaglar at the non-inferiority margin of –0.4%. Secondary efficacy outcomes included 7-point SMBG, intra-patient variability (measured by SD of FBG), change in A1C from baseline to weeks 4, 8, 12, 16, 20, and 24 (or LOCF), proportion of patients achieving A1C targets of < 7% and ≤ 6.5%, basal insulin dose at end point, and body weight. Pre-specified PRO measures were the ITSQ and ALBSS.

Characteristics		Details for ELEMENT 2 (ABEC)
		Safety outcomes included AEs including SAEs, allergic events, injection-site reactions, and hypoglycemic events. Insulin antibody levels were also assessed.
NOTES	**Publications**	Rosenstock J., Hollander P., Bhargava A., Ilag L.L., Pollom R.K., Zielonka J.S., Huster W.J., Prince M.J. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naive or previously treated with insulin glargine: A randomized, double-blind controlled trial (the ELEMENT 2 study). Diabetes, Obesity and Metabolism. 2015 Aug; 17 (8): 734-741. • clinicaltrials.gov identification code: NCT: 01421459

A1C = glycated hemoglobin; AE = adverse event; ALBSS = Adult Low Blood Sugar Survey; BMI = body mass index; FBG = fasting blood glucose; GLP = glucagon-like peptide; ITSQ = Insulin Treatment Satisfaction Questionnaire; LOCF = last observation carried forward; OAD = oral antidiabetes drug; PRO = patient-reported outcome; SAE = serious adverse event; SD = standard deviation; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus; WHO = World Health Organization; vs. = versus.

Intervention and Comparators

- Patients were randomly allocated to treatment with Basaglar once daily or Lantus once daily; patients in both treatment arms continued with pre-study oral antidiabetes drugs (including sulfonylureas) throughout the 24-week treatment period, unless described otherwise for certain conditions pre-specified in the protocol.
- In terms of dose, patients who were already on Lantus at study entry were converted on a unit-to-unit basis to Basaglar or Lantus. Patients who were insulin-naive at baseline were started on a basal insulin dose of Basaglar or Lantus of 10 units per day and followed a titration schedule whereby dose was increased by 1 unit per day (2 units every other day in Korea and Taiwan) until FBG ≤ 100 mg/dL (5.6 mmol/L) was achieved.
- Patients continued to take pre-study oral antidiabetes drugs at the same dose during the study. If in emergencies it was necessary for a patient to change his or her dose of oral antidiabetes drugs and/or be treated with a non-study insulin, this was permitted for up to 14 consecutive days. If such a situation occurred more than once during the study, or lasted longer than 14 consecutive days, a decision to keep the patient in the study was to be made after consultation between the investigator and the manufacturer. Dose changes for sulfonylureas were permitted for patients who experienced hypoglycemic events during the study. All concomitant medications that were part of routine care were permitted for use during the study.
- Lantus and oral antidiabetes drugs were administered and dosed in accordance with local product labelling.
- EU- and US-approved Lantus were used in the trial.
- Both Basaglar and Lantus are clear, colourless solutions. In this study, both insulins were administered using covered vials and syringes. Since the administered insulins looked identical, double-dummy controls were not required.

Outcomes

- The pre-specified primary efficacy outcome was change in A1C from baseline to end point (week 24 or LOCF).
- The primary treatment comparison was to compare Basaglar versus Lantus at the non-inferiority margin of 0.4%.
- Secondary efficacy outcomes included seven-point SMBG, intra-patient variability (measured by SD of FBG), change in A1C from baseline to weeks 4, 8, 12, 16, 20, and 24 (or LOCF), proportion of patients achieving A1C targets of < 7% and ≤ 6.5%, basal insulin dose at end point, and body weight. Pre-specified patient-reported outcome (PRO) measures were the ITSQ and ALBSS.

- Safety outcomes included AEs including SAEs, allergic events, injection-site reactions, and hypoglycemic events. Insulin antibody levels were also assessed.

Statistical Analyses

(CTD, Module 2.7.6 Synopses of Individual Studies, p. 49)

- The primary analysis model was an ANCOVA with country, sulfonylurea use (yes, no), time of basal insulin injection (daytime, evening/bedtime), and treatment as fixed effects, and baseline A1C as a covariate.
- The primary treatment comparison was to compare Basaglar versus Lantus at the non-inferiority margin of 0.4%. If the upper limit of the 95% CI on the change in A1C from baseline to 24-week end point (LOCF) for Basaglar was less than 0.4%, then Basaglar was declared non-inferior to Lantus.
- The LS mean and SE derived from the ANCOVA model for each treatment were used to test for non-inferiority. Type III sums of squares were used to make the treatment comparisons. If the 0.4% non-inferiority margin was met, then the upper limit of the 95% CI was compared with the 0.3% non-inferiority margin. This gate-keeping procedure controlled the family-wise Type1 error rate at a one-sided 0.025 level.
- A key secondary treatment comparison was to compare Lantus versus Basaglar at the non-inferiority margin of –0.4%. If the lower limit of the 95% CI on the change in A1C from baseline to 24-week end point (LOCF) for Basaglar versus Lantus was greater than –0.4%, then Lantus insulin glargine was declared non-inferior to Basaglar. The LS mean and SE derived from the ANCOVA model for each treatment was used to test non-inferiority. If Basaglar was declared non-inferior to Lantus in the primary treatment comparison and Lantus was declared non-inferior to Basaglar in the secondary treatment comparison, then Basaglar was considered to have equivalent efficacy to Lantus. The analysis of the continuous secondary efficacy measurements used the ANCOVA model with the FAS population.
- All tests of treatment effects and interactions between treatment groups were conducted at two-sided alpha level of 0.05.
- Subgroup analyses for the primary end point were performed according to A1C at study entry (< 7% versus ≥ 7% and < 8.5% versus ≥ 8.5%), basal insulin at study entry (insulin glargine versus none), body mass index (BMI) at study entry (< 25 kg/m^2 versus ≥ 25 kg/m^2 and < 30 kg/m^2 versus ≥ 30 kg/m^2), age (< 65 years versus ≥ 65 years and < 75 years versus ≥ 75 years), use of sulfonylureas (yes versus no), time of basal insulin injection (daytime versus evening/bedtime), sites with US-approved Lantus insulin glargine versus sites with EU-approved Lantus, gender, country, and race.
- The primary analysis was intention-to-treat.

TABLE 15: SUMMARY OF STATISTICAL ANALYSES IN THE ELEMENT 2 (ABEC) STUDY

Trial ID	Hypothesis Objective	Sample Size, Power Calculation	Data Management, Patient Withdrawals
ABEC	Hypothesis: Basaglar once daily was non-inferior to Lantus insulin glargine once daily as measured by change in A1C from baseline to week 24, when used in combination with OADs.	To show non-inferiority of Basaglar to Lantus insulin glargine at the non-inferiority margin of 0.4%, a total of 568 completers (284 from each treatment arm) were required, but assuming a 15% dropout rate at 24 weeks, the required number of randomized patients was 334 per arm (668 total). The same sample size was needed to show non-inferiority of Basaglar to Lantus at the 0.3% non-inferiority margin with 90% power.	Missing data were handled using the LOCF approach.

A1C = glycated hemoglobin; LOCF = last observation carried forward; OAD = oral antidiabetes drug.

b) Results

Baseline Characteristics

TABLE 16: BASELINE PATIENT DEMOGRAPHICS AND PATIENT CHARACTERISTICS FOR THE ELEMENT 2 TRIAL

Baseline Characteristic	Basaglar n = 376	Lantus n = 380
Mean (SD) age (years)	59.0 (10.2)	58.7 (10.0)
Male, n (%)	179 (47.6)	199 (52.4)
Race, n (%)		
American Indian/Alaska Native	17 (4.5)	21 (5.5)
Asian	29 (7.7)	35 (9.2)
Black/African American	26 (6.9)	32 (8.4)
Multiple	2 (0.5)	1 (0.3)
White	302 (80.3)	291 (76.6)
Mean (SD) duration of diabetes (years)	11.7 (6.8)	11.2 (6.8)
Mean (SD) A1C, %	8.3 (1.1)	8.3 (1.1)
Time of basal injection, n (%)		
Daytime	187 (49.7)	188 (49.5)
Evening/bedtime	189 (50.3)	192 (50.5)
Use of sulfonylurea, n (%)		
Yes	315 (83.8)	315 (82.9)
No	61 (16.2)	65 (17.1)

A1C = glycated hemoglobin; SD = standard deviation

Baseline patient demographics and characteristics were well balanced between the two treatment arms. Overall the mean age was 58.8 years and the mean duration of type 2 diabetes was 11.5 years. Additionally, 50% of patients were male and 78% patients were white.

At study entry, all patients were receiving two or more oral antidiabetes drugs; prior to randomization, 82.1% (n = 621) of patients were on two oral antidiabetes drugs (n = 298 [79.3%] in the Basaglar group and n = 323 [85.0%] in the Lantus group) and a total of [redacted]. In terms of basal insulin therapy prior to study entry, 155 (41.2%) out of 376 patients in the Basaglar

treatment group and 144 (37.9%) out of 380 patients in the Lantus group were taking Lantus prior to study entry. All other patients were not taking basal insulin prior to enrolment in the trial.

Patient Disposition

A total of 759 patients were randomly allocated to treatment and three patients discontinued before receiving the first dose of study drug, leaving a total of 756 patients for inclusion in the FAS population (n = 376 patients in the Basaglar group and n = 380 patients in the Lantus group).

TABLE 17: SUMMARY OF PATIENT DISPOSITION FOR ELEMENT 2 (ABEC)

Disposition	ELEMENT 2	
	Basaglar	Lantus
Screened, N	N = 1,026	
Randomized, N	N = 759	
Discontinued, N (%)	42 (11.2%)	52 (13.7%)
WDAEs, N (%)	5 (1.3%)	10 (2.6%)
Withdrawal due to SAEs, N (%)	4 (1.1%)	5 (1.3%)
Lost to follow-up, N (%)	7 (1.9%)	9 (2.4%)
Intention-to-treat, N	376	380
Per-protocol, N	334	328
Safety, N	376	380

SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Efficacy Results

At week 24, both groups had significant decreases from baseline in A1C with values of −1.29% for the Basaglar-treated group and −1.34% for the Lantus group. The LS mean (95% CI) between-group difference in terms of A1C change from baseline to end point was 0.052% (−0.070 to 0.175%). Basaglar was found to be non-inferior to Lantus at the 0.4% and 0.3% non-inferiority margins. Non-inferiority of Lantus to Basaglar was also demonstrated as a secondary end point and thus Basaglar and Lantus were consequently considered to have similar efficacy.

TABLE 18: CHANGE IN A1C FROM BASELINE TO END POINT IN ELEMENT 2

	Baseline (SE)	End Point (SE)	LS Mean Change	Mean Difference (95% CI)
Basaglar	8.35 (0.06)	7.04 (0.06)	−1.29 (0.06)	0.052 (−0.070 to 0.175)
Lantus	8.31 (0.06)	6.99 (0.06)	−1.34 (0.06)	

A1C = glycated hemoglobin; CI = confidence interval; LS = least squares; SE = standard error.
Source: ABEC Clinical Study Report (March 12, 2013), Table 11.2 (page 90).

TABLE 19: SUMMARY OF A1C CHANGE IN ELEMENT 2 (PER-PROTOCOL)

	Baseline (BL)	24-Week	
		End Point (EP) (LOCF) (%)	Δ BL to EP (LOCF) (%)
Basaglar			
n[a]	314	314	314
LS mean	8.351	7.018	–0.1332[b]
Lantus			
n[a]	308	308	308
LS mean	8.348	6.902	–1.448[b]
LS mean diff (95% CI)			0.116 (–0.101 to 0.242)

CI = confidence interval; diff = difference; LOCF = last observation carried forward; LS = least squares.
[a] Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
[b] Within-treatment $P < 0.001$.
Source: Table 2.7.3.6 in Module 2.7.3 Summary of Clinical Efficacy.

Analysis of change in A1C from baseline to other time points showed that both groups had significant decreases from baseline at weeks 4, 8, 12, 16, 20, and 24 with the between-group difference at each intermediate time point meeting the non-inferiority margin of 0.3%. At study end (LOCF), a total of 48.8% of patients in the Basaglar group and 52.2% of patients in the Lantus group achieved A1C < 7.0%. Similarly, the proportions of patients achieving A1C of ≤ 6.5% at end point (LOCF) was 26.8% in the Basaglar-treated group and 30.4% in the Lantus-treated group, and the between-group difference was not statistically significant.

Seven-point SMBG profiles showed that at end point (LOCF), the LS mean blood glucose value at the morning two-hour post-prandial time point was lower for Basaglar (8.07 mmol/L) than for Lantus (8.40 mmol/L) with an LS mean difference of −0.33 mmol/L ($P = 0.050$). Mean blood glucose levels were also lower in the Basaglar-treated arm at the midday pre-meal time point (6.81 mmol/L for Basaglar versus 7.12 mmol/L for Lantus; LS mean difference of −0.31 mmol/L; $P = 0.04$). There were no significant between-group differences at other time points. In both treatment groups, the basal insulin dose increased during the 24-week treatment period, with the increases from baseline to end point being similar in both treatment arms (Table 20).

TABLE 20: SUMMARY OF DAILY INSULIN DOSE CHANGE IN ELEMENT 2

	ELEMENT 2 (24-Week) N = 756	
	Basaglar (N = 376)	Lantus (N = 380)
Basal insulin dose (U/day)		
No. of patients[a]	374	379
Mean baseline	15.4	12.0
LS mean change from baseline[b]	32.3	32.6
Total insulin dose (U/day)		
# of patients[a]	NA	NA
Mean baseline	NA	NA
LS mean change from baseline[b]	NA	NA

LS = least squares; NA = not available.
[a] Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
[b] Change from baseline to end point values are LS means, reflecting adjustment for the design factors of the study. Baseline values are unadjusted means.

TABLE 21: SELECTED PATIENT-REPORTED OUTCOMES IN ELEMENT 2

	Basaglar (N = 376)	Lantus (N = 380)	Statistical Comparison
ALBSS total score – 24 weeks (LOCF) (n = 368,371)	16.53 (1.32)	16.92 (1.33)	*P* = 0.765
ITSQ total – 24 weeks (LOCF) (n = 368,372)	78.54 (1.21)	79.06 (1.22)	*P* = 0.662

A1C = glycated hemoglobin; ALBSS = Adult Low Blood Sugar Survey; ITSQ = Insulin Treatment Satisfaction Questionnaire; LOCF = last observation carried forward; LS = least squares.
Note: Data are LS mean (standard error). LS means are determined by analysis of covariance (ANCOVA) and adjusted for baseline A1C, country, sulfonylurea use, time of basal insulin injection, and treatment.

Subgroup of patients switching from Lantus to Basaglar: In ELEMENT 2, no significant treatment differences were observed for change in A1C from baseline to end point (LOCF), the proportion of patients achieving glycemic targets, mean FBG and daily mean BG, basal insulin dose, and weight change.

TABLE 22: BASAL INSULIN DOSE — CHANGE FROM BASELINE TO END POINT (LAST OBSERVATION CARRIED FORWARD) BY ENTRY BASAL INSULIN TREATMENT (ELEMENT 2)

	Basaglar		Lantus		*P* Value
	N	Δ From Baseline LS Mean (SE)	N	Δ From Baseline LS Mean (SE)	
Basal insulin dose (U/day)					
Pre-study Lantus	154	20.25 (3.12)	144	15.58 (3.20)	
Insulin-naive	220	39.76 (2.79)	235	41.78 (2.72)	0.171

LS = least squares; SE = standard error.

Safety Results

There were two deaths during ELEMENT 2, with one death occurring in each treatment arm (one patient had a myocardial infarction with fatal outcome and one patient had lung adenocarcinoma with fatal outcome). Overall, 33 patients (4.4%) experienced one or more SAEs during the treatment period (15 patients [4.0%] in the Basaglar group and 18 patients [4.7%] in the Lantus group), with severe hypoglycemia being the most frequently reported SAE. Additionally, nine patients experienced SAEs that

led to treatment discontinuation (none of which were considered to be related to the study drug). In total, 17 patients (six patients [1.6%] in the Basaglar arm and 11 patients [2.9%] in the Lantus arm) experienced AEs that led to discontinuation. No notable differences were observed in terms of TEAEs between treatment groups, with the exception of vascular disorders, where the incidence (primarily hypertension) was higher on Basaglar than on Lantus (21 patients [5.6%] versus nine patients [2.4%]; *P* = 0.026).

A total of 588 patients (78.5%) reported 7,409 hypoglycemic events (all categories; defined as blood glucose level ≤ 70 mg/dL [3.89 mmol/L]) during the study. There were no significant between treatment group differences in the incidence of total hypoglycemic events at end point (LOCF) or at any other intermediate time point during the study. In total, four patients (0.5%) reported nine severe hypoglycemic events.

Analysis of anti-insulin antibody levels showed that at week 4, there was a significant difference between groups in terms of the proportion of patients with detectable anti-insulin antibodies (Basaglar: 26 patients [7.2%]; Lantus: 13 patients [3.6%]; *P* = 0.047). However, there were no significant differences at any other time point, at study end (LOCF) or overall. At study end point (LOCF) 5.8% (n = 42) of patients had TEAR, consisting of 6.6% (n = 22) of patients in the Basaglar group and 5.5% (n = 20) of patients in the Lantus insulin glargine group (*P* = 0.874). Overall, 10.8% (n = 79) of patients (12.3% [n = 45] in the Basaglar group and 9.3% [n = 34] in the Lantus insulin glargine group; *P* = 0.233) had TEAR.

4.2.4 Summary of Safety

TABLE 23: OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS IN ELEMENT 1 AND ELEMENT 2

System Organ Class/Adverse Events[a]	ELEMENT 1 (ABEB) (52 Weeks)		ELEMENT 2 (ABEC) (24 Weeks)	
	Basaglar, n (%) n = 268	Lantus, n (%) N = 267	Basaglar, n (%) n = 376	Lantus, n (%) n = 380
Patients with ≥ 1 TEAE	167 (62.3)	166 (62.2)	196 (52.1)	184 (48.4)
Nasopharyngitis	43 (16.0)	45 (16.9)	21 (5.6)	22 (5.8)
Upper respiratory tract infection	22 (8.2)	21 (7.9)	19 (5.1)	15 (3.9)
Hypoglycemia[b]	13 (4.9)	12 (4.5)	—	—
Diarrhea	12 (4.5)	10 (3.7)	9 (2.4)	14 (3.7)
Hypertension[b]	9 (3.4)	5 (1.9)	8 (2.1)	3 (0.8)
Influenza	5 (1.9)	5 (1.9)	7 (1.9)	11 (2.9)
Back pain	10 (3.7)	9 (3.4)	9 (2.4)	10 (2.6)

TEAE = treatment-emergent adverse event.
[a] Occurring in > 3% patients in either treatment group.
[b] As reported by the investigators (no specific definition is applicable for these outcomes for this table; see Table 24 for hypoglycemia data specifically defined by the study protocol).

a) Definitions of Hypoglycemia in ELEMENT 1 and ELEMENT 2

Total hypoglycemia: Events meeting the criteria for severe hypoglycemia, documented symptomatic hypoglycemia with BG ≤ 3.9 mmol/L (70 mg/dL), asymptomatic hypoglycemia with BG ≤ 3.9 mmol/L (70 mg/dL), probable symptomatic hypoglycemia, or unspecified hypoglycemia with BG ≤ 3.9 mmol/L (70 mg/dL).

Severe hypoglycemia: Symptoms requiring assistance of another person, including severe hypoglycemia events with BG ≤ 3.9 mmol/L (70 mg/dL), BG < 3.0 mmol/L (54 mg/dL), BG missing, or BG not aligned with severe symptoms.

Documented symptomatic hypoglycemia: Any event during which typical symptoms of hypoglycemia were accompanied by a measured BG concentration ≤ 70 mg/dL (3.9 mmol/L).

TABLE 24: MOST CLINICALLY RELEVANT HYPOGLYCEMIA EVENTS — ELEMENT 1 (52 WEEKS), FULL ANALYSIS SET

	Basaglar N = 268		Lantus N = 267		*P* Value
	N (%)	Events	N (%)	Events	
Total hypoglycemia	256 (95.5)	19,541	259 (97.0)	20,852	0.495
Severe hypoglycemia	10 (3.7)	13	11 (4.1)	16	0.828
Documented symptomatic hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 25: MOST CLINICALLY RELEVANT HYPOGLYCEMIA EVENTS — ELEMENT 2 (24 WEEKS), FULL ANALYSIS SET

	Basaglar N = 376		Lantus N = 380		*P* Value
	N (%)	Events	N (%)	Events	
Total hypoglycemia	296 (79.4)	3,564	292 (77.7)	3,845	0.594
Severe hypoglycemia	2 (0.5)	7	2 (0.5)	2	NR
Documented symptomatic hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported.

a) Safety Evaluation Plan

Phase 3 Study Safety Evaluation Plan

(CTD, Module 2.7.4.1.1.1)

Safety in both phase 3 studies was assessed by evaluation of data for AEs (all-cause and treatment-emergent), hypoglycemia, clinical laboratory measurements including anti-insulin antibodies, and vital signs. Baseline was defined as the last non-missing observation during the baseline period. End point was the last non-missing observation in the treatment period in accordance with LOCF methodology; in the integrated analyses, end point (LOCF) included the last non-missing observation up to 52 weeks in Study ABEB, and the last non-missing observation up to 24 weeks in Study ABEC. Only patients with non-missing baseline and non-missing end point were included in the analyses of continuous data. The term overall is defined as including all post-baseline events that occurred over 52 weeks of treatment in Study ABEB and all post-baseline events that occurred over 24 weeks of treatment in Study ABEC.

[redacted]

[redacted]

Clinical Pharmacology Safety Evaluation Plan
(CTD, Module 2.7.4.5.10.1)
The safety data presented includes patients who received at least one dose of Basaglar or Lantus.

To assess the safety and tolerability of Basaglar and Lantus in healthy patients, safety data (primarily TEAEs and vital signs data) were summarized across the healthy patient studies (ABEO, ABEA, ABEN, ABEI, and ABEM) as follows:

- All dose levels combined (0.3, 0.5, and 0.6 U/kg) (Studies ABEO, ABEA, ABEN, ABEI, and ABEM)
- The 0.5 U/kg dose level alone (Studies ABEO, ABEA, ABEN, and ABEI)
- The 0.3 U/kg and 0.6 U/kg dose levels alone and combined (Study ABEM).

A comparison of EU- and US-approved Lantus in Study ABEN was conducted. As one of the comparative PK and PD studies to establish the scientific bridge, ABEN was deemed important to include in the evaluation of safety. To assess the safety and tolerability of Basaglar and Lantus in patients with type 1 diabetes mellitus (Study ABEE), safety data were summarized at the single dose level examined (0.3 U/kg).

b) Safety Populations Evaluated
The largest safety population addressed in the clinical safety summary is from the two phase 3 clinical studies. A total of [redacted] patients with type 1 diabetes mellitus or type 2 diabetes mellitus were randomly assigned to treatment in the phase 3 studies. Of these patients, [redacted] patients received at least one dose of randomly assigned study drug, comprising the FAS, and serving as the population of interest for analyses in this summary document (CTD Module 2.7.4.1.3.1). The mean duration of exposure for patients in the phase 3 studies was [redacted] weeks and [redacted] weeks for the Basaglar and Lantus groups, respectively. Approximately [redacted] of patients were exposed to study drug for at least 24 weeks (CTD Module 2.7.4.1.2).

The safety population in clinical pharmacology studies (Studies ABEO, ABEA, ABEN, ABEI, and ABEM) were as follows: all Basaglar (N = [redacted]), EU Lantus (N = [redacted]), US Lantus (N = [redacted]) (CTD Module 2.7.4, Table 2.7.4.53).

c) Overview of Safety
(See Appendix 1: Additional Data, Table 2.7.4.7 for AE overview in FAS).
All AEs were included in the analyses, regardless of the investigator's or the sponsor's judgment about causality. TEAEs were defined as events that first occurred or worsened in severity on or after the date of first dose (that is, the date of first injection of study treatment) and on or prior to the date of the last visit of the treatment or extension period. AEs were coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1.

There were no statistically significant treatment differences for the incidence of SAEs, discontinuations due to AEs, TEAEs (including those possibly related to study drug, procedure, or disease), injection-site AEs, or TEAEs captured by the special topic assessment of allergic events.

TEAEs were reported by [redacted] Basaglar patients and [redacted] Lantus patients with [redacted] Basaglar patients and [redacted] Lantus patients reporting TEAEs that the investigator considered to be

possibly related to study drug. SAEs were experienced by [redacted] Basaglar patients and [redacted] Lantus patients. Events in three patients resulted in death (Basaglar: [redacted]; Lantus: [redacted]; all were assessed by the respective investigators as not related to study drug or study procedures). A total of 25 patients (Basaglar: [redacted]; Lantus: [redacted]) discontinued due to an AE (Basaglar: [redacted] patients [redacted]; Lantus: [redacted] patients [redacted]). Similar percentages of patients in both treatment groups reported TEAEs captured by the special topic assessment of allergic events (Basaglar: [redacted] patients [redacted]; Lantus: [redacted] patients [redacted]) (CTD Module 2.7.4.2.1).

For further details on TEAEs, please see CTD Module 2.7.4.2.1.1, Treatment-Emergent Adverse Events.

4.3 Pharmacokinetics

TABLE 26: SUMMARY OF PHARMACOKINETICS FROM PIVOTAL ABEO TRIAL

Pharmacokinetics	Basaglar 0.5 U/kg Geometric Means	US Lantus 0.5 U/kg Geometric Means	Ratio, 90% CI for Ratio of Geometric Means
AUC(0-24) pmol.h/L[a]	1,715.51	1,907.09	0.9 (0.85 to 0.95)
C_{max} pmol/L[a]	102.91	112.19	0.92 (0.87 to 0.97)
T_{max} (h)[b]	12.0	12.0	NA
T1/2 (h)[b]	10.0	11.6	NA
Bioavailability	Not assessed in ABEO		
Degradation	Not assessed in ABEO		

AUC = area under the curve; CI = confidence interval; C_{max} = maximum concentration; NA = not assessed; T1/2 = elimination half-life; T_{max} = time to maximum plasma concentration.
[a] CTD: Module 2.7.1; Table 2.7.1.4, page 15.
[b] Clinical Study Report for ABEO. Table ABEO 7.1, page 24.

4.3.1 Summary of Absorption/Bioavailability

The relative bioavailability of Basaglar to Lantus was close to 1, with the 90% CI of the LS mean ratio of AUC(0-24) of Basaglar to Lantus being contained within the window of 0.8 to 1.25 in healthy patients following a single dose administration of 0.5 units/kg subcutaneously.[viii]

For a summary of pharmacokinetics from the three phase 1 studies, see Appendix 1: Additional Data, Table 3.

4.4 Immunogenicity

In both phase 3 trials, immunogenicity of Basaglar was assessed via the measurement of the proportion of patients with antibodies and the proportion of patients with TEAR (defined as an increase of ≥ 1% in absolute anti-insulin antibody levels and a relative increase of ≥ 30% from baseline for patients who were anti-insulin antibody-positive at baseline, or previously antibody-negative patients who became antibody-positive during the course of the study). In ELEMENT 1, the overall incidences of TEAR during the first 24 weeks of treatment were similar between Basaglar and Lantus: 22% (57/265) in patients treated with Basaglar and 19.5% (52/267) in patients treated with Lantus (*P* = 0.542). Overall incidences of TEAR during 52 weeks of treatment were also similar between treatment groups (Basaglar: 30.9% [82/265]; Lantus: 25.8% [69/267], *P* = 0.212). There were no significant differences in the proportion of patients with detectable antibodies between treatment groups at any visit or end point (LOCF). The overall incidences of TEARs after 24 and 52 weeks of treatment were similar between Basaglar and Lantus treatment groups. In addition, no significant treatment-by-TEAR interactions were identified for any of the clinical outcomes tested (including change from baseline in A1C, rate of total hypoglycemia, and basal insulin dose). The incidence of potential antibody-related AEs including allergic events and injection-

site reactions was also assessed in both phase 3 studies: no notable differences between treatments were observed and no safety concerns were identified.

5. CRITICAL APPRAISAL OF CLINICAL STUDIES

5.1 Internal Validity

The manufacturer summarized one PK/PD study (ABEO: N = 91 healthy patients) and two phase 3 studies (ELEMENT 1/ABEB: N = 536 patients with type 1 diabetes mellitus; ELEMENT 2/ABEC: N = 759 patients with type 2 diabetes mellitus). The manufacturer performed several other PK/PD trials but these were not included in the manufacturer's submission to CADTH. Based on these data, Health Canada stated that "the therapeutic benefits seen in the pivotal [Basaglar] studies are comparable to the reference product, Lantus."[5] Studies performed by the manufacturer are listed in Table 27. A grey literature search did not reveal any additional relevant studies.

TABLE 27: OVERVIEW OF BASAGLAR STUDIES[6]

Study Alias	Objective	Study Population	Number of Subjects Randomized
Phase 1 Studies			
ABEO	Comparison of the PK and PD of LY2963016 and US-approved LANTUS®	Healthy subjects	91
ABEA	Comparison of the PK and PD of LY2963016 and EU-approved LANTUS®	Healthy subjects	80
ABEN[a]	Comparison of the PK and PD of EU- and US-approved LANTUS®	Healthy subjects	40
ABEI	Relative bioavailability of LY2963016 to EU-approved LANTUS®	Healthy subjects	16
ABEE	Comparison of the PD of LY2963016 and EU-approved LANTUS®	Patients with T1DM	20
ABEM	Relative bioavailability of LY2963016 to EU-approved LANTUS®	Healthy subjects	24
Phase 3 Studies			
ABEB	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with pre-meal insulin lispro	Patients with T1DM (open-label)	536 LY2963016: 269 LANTUS®: 267 (US-approved: 96/ EU-approved: 171)
ABEC	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with OAMs	Patients with T2DM (double-blind)	759 LY2963016: 379 LANTUS®: 380 (US-approved: 215/ EU-approved: 165)

EU = European Union; HbA1c = glycated hemoglobin; LY2963016 = Basaglar; OAM = oral antihyperglycemic medication; PD = pharmacodynamic; PK = pharmacokinetic; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

5.1.1 ABEO Study (Phase 1 Study) — Reviewer Comments

ABEO was a randomized, double-blind, single dose (0.5 U/kg) two-treatment, four-period, crossover, replicate-treatment euglycemic clamp study to evaluate the PK and PD similarity of Basaglar and US-approved Lantus. ABEO was considered to be a pivotal study by the manufacturer. Patients were randomly assigned to one of two dosing sequences and received 0.5 U/kg Lantus on two occasions and 0.5 U/kg Basaglar on two occasions.

Health Canada considered the ABEO study, together with the ABEA and ABEN studies, for its PK/PD assessment. Health Canada reviewers made the following observations regarding these PK/PD data:[5]

- Pharmacokinetics: Basaglar, US-approved Lantus, and EU-approved Lantus have comparable PK properties based on the mean area under the plasma concentration time curve (AUC) over the dosing interval (0–24 hours) and the peak plasma concentration.
- Pharmacodynamics: In each of the PK/PD studies, the effect of insulin on blood glucose was investigated using a euglycemic clamp procedure in which the GIR was varied over 24 hours in order to maintain a euglycemic state. The parameters of total glucose infused and maximum glucose infusion rate were the primary end points compared to investigate PD similarity. Basaglar was shown to have comparable PD properties to both US and EU Lantus. In addition, US and EU Lantus were also found to be comparable to each other.

5.1.2 ELEMENT 1/ABEB Type 1 Diabetes Mellitus Phase 3 Study[7] — Reviewer Comments

ELEMENT 1 was a randomized, multinational, open-label, non-inferiority study in patients with type 1 diabetes mellitus. No information regarding methods of randomization or allocation concealment was provided. The mean age of patients was 41 years, 58% were male, mean A1C at baseline was 7.8%, and more than 80% of patients were taking Lantus prior to study entry. Pre-study basal insulin was converted on a unit-to-unit basis to either Lantus or Basaglar at randomization.

Of the short list of baseline characteristics provided by the manufacturer, there were no major differences observed except for A1C at baseline, which was more commonly < 7.0% in the Basaglar group compared with the Lantus group. Mean A1C at baseline was the same in the Basaglar and Lantus groups. The baseline differences in A1C may have confounded the analysis of A1C at weeks 24 and 52, though the manufacturer did include baseline A1C as a covariate in the statistical analysis of the primary outcome, and this should have minimized bias related to the imbalance.

ELEMENT 2 was a blinded study, but the manufacturer did not explain why ELEMENT 1 did not use blinding. The open-label design may have resulted in imbalance in prognostic factors between the treatment groups as the trial progressed. The study publication states that dose adjustments of basal insulin were made by investigators to achieve targets of A1C < 7.0% and FBG ≤ 6.0 mmol/L and preprandial capillary blood glucoses 3.9 to 7.2 mmol/L.[7] The knowledge of treatment assignment may have changed the behaviour of treating physicians and patients. This could have had a differential impact on dosing of insulin during the trial (e.g., reporting of symptoms of hypoglycemia, different thresholds for reporting AEs, frequency of blood glucose testing). This could have biased the results, but the direction of the bias is unknown.

The primary outcome was change in A1C from baseline to week 24, and Basaglar was compared to Lantus using the non-inferiority margins of 0.4% and 0.3%. A margin of 0.3% or 0.4% is what is typically accepted by the FDA for non-inferiority testing of treatments for diabetes mellitus.[8]

Approximately 5% of patients discontinued the study by week 24 and 8% discontinued by week 52. Overall withdrawal rates were similar between the two treatment groups, but the manufacturer did not provide detailed reasons for withdrawals, so the impact of withdrawals on internal validity cannot be assessed. Withdrawals due to adverse events (WDAEs) were slightly higher in the Basaglar treatment group (6 [2.2%]) compared with the Lantus treatment group (2 [0.7%]) at week 52.

The primary outcome of the study was LS mean change in A1C from baseline to week 24. The difference in A1C between treatments from baseline to week 24 was 0.11% (95% CI, −0.005% to 0.217%; $P < 0.061$). Basaglar was found to be non-inferior to Lantus at the 0.4% non-inferiority margin at this time point and also at the week 52 time point. The primary end point results were obtained using a modified intention-

to-treat (ITT) population applying the LOCF principle for missing data. The manufacturer also presented the primary outcome results based on the per-protocol population, and the results were similar to the results of the ITT analyses. This is a significant omission from the manufacturer's submission, because using the ITT and applying LOCF may not be the most conservative method for non-inferiority testing.[9]

Week 24 results for mean body weight, mean daily insulin dose (prandial and basal), mean FBG, and daily mean blood glucose were similar for both treatment groups. The results for these secondary outcomes were not tested for non-inferiority, but were largely consistent with the results with primary outcome. One exception to this was that there were statistically significant differences observed at bedtime and 3:00 a.m. for the SMBG measurements (Basaglar versus Lantus).

There were no statistically significant differences in the incidence of AEs and SAEs. Injection-site reactions occurred at similar rates in the Basaglar and Lantus groups. The overall and nocturnal hypoglycemia rates (events/person/year) were similar in the Basaglar and Lantus groups at weeks 24 and 52. The percentage of patients with detectable antibodies to insulin was similar in the Basaglar and Lantus groups.

5.1.3 ELEMENT 2/ABEC Type 2 Diabetes Mellitus Phase 3 Study[10] — Reviewer Comments

ELEMENT 2 was a randomized, multinational, blinded, non-inferiority study in patients with type 2 diabetes mellitus. No information regarding methods of randomization or allocation concealment was provided. The mean age of patients was 59 years, approximately 51% were male, mean A1C at baseline was 8.3%, and approximately 40% of patients were taking a basal insulin (Lantus) prior to study entry. Pre-study basal insulin was converted on a unit-to-unit basis to either Basaglar or Lantus at randomization. Patients were started on Basaglar or Lantus 10 U/day if they had not used insulin prior to the study.

Of the short list of baseline characteristics provided by the manufacturer, there were no major differences observed between the Basaglar and Lantus groups.

Approximately 12% of patients discontinued the study by week 24. Overall withdrawal rates were similar between the two treatment groups, but the manufacturer did not provide detailed reasons for withdrawals, so the impact of withdrawals on internal validity could not be assessed. WDAEs were slightly lower in the Basaglar treatment group (5 [1.3%]) compared with the Lantus treatment group (10 [2.6%]) at week 24. Withdrawals were quite high for a short study in a chronic disease condition, but the impact of these withdrawals on study outcomes is unknown because the manufacturer did not provide any sensitivity analyses of the results based on different assumptions about the missing data.

The primary outcome was change in A1C from baseline to week 24 and Basaglar was compared with Lantus using the non-inferiority margins of 0.4% and 0.3%. The difference in A1C between treatments from baseline to week 24 was 0.052% (95% CI, −0.070 to 0.175%). Basaglar was found to be non-inferior to Lantus at the 0.4% and 0.3% non-inferiority margins at week 24. The primary end point results were obtained using a modified ITT population applying the LOCF principle for missing data. The manufacturer also presented the primary outcome results based on the per-protocol population, and the results were similar to the results of the ITT analyses.

Week 24 results for change in body weight, mean daily insulin dose (U/kg/day), and FBG change from baseline were similar for both treatment groups. The results for these secondary outcomes were mostly congruent with the results of the primary outcome. Similar to the observations in ELEMENT 1, there were small but statistically significant differences in SMBG at two time points during the day (Basaglar versus Lantus).

Similar to the findings in ELEMENT 1, there were no statistically significant differences in the incidence of AEs and SAEs between the treatment groups. Injection-site reactions were rare and occurred at similar rates in the Basaglar and Lantus groups (~1%). The overall and nocturnal hypoglycemia rates (events/person/year) were similar in the Basaglar and Lantus groups at week 24. The percentage of patients with detectable antibodies to insulin was similar in the Basaglar and Lantus groups at week 24.

5.2 External Validity

5.2.1 ABEO Study (Phase I Study) — Reviewer Comments

The participants in this study were healthy volunteers and were predominantly male (94%). There was a predominance of Asian patients in the study (99%). While the ABEO study population does not reflect the ethnic diversity of the Canadian population, there is no strong reason to believe that the pharmacodynamic results of this bioequivalence study as observed in Asian patients would not also apply to non-Asian patients.

5.2.2 ELEMENT 1 (Type 1 Diabetes Mellitus) and ELEMENT 2 (Type 2 Diabetes Mellitus) Phase 3 Studies[7,10] — Reviewer Comments

The majority of patients in these studies were white and also included people of Asian, Black, and Native-American races. There were no Canadian study sites in these trials; however, according to the clinical expert for this review, the ethnic makeup of the study populations is a reasonable reflection of patients in Canada who are candidates for treatment with Basaglar. Mean BMI was 26 kg/m^2 in the type 1 diabetes mellitus study and 32 kg/m^2 in the type 2 diabetes mellitus study. The type 1 diabetes mellitus study was longer (52 weeks) than the type 2 diabetes mellitus study (24 weeks) and therefore provides a longer-term perspective on relative efficacy and harms. Patients in the type 1 diabetes mellitus study had used basal and mealtime insulin for at least one year. Patients in the type 2 diabetes mellitus study were receiving two or more oral antidiabetes medicines at stable doses for at least 12 weeks prior to study entry. The timing of basal injections differed between the type 1 diabetes mellitus and type 2 diabetes mellitus studies. This was also reflective of what would normally be expected in the Canadian population with diabetes, with a higher proportion of patients receiving basal insulin in the morning in type 2 diabetes mellitus, relative to type 1 diabetes mellitus. The high prevalence (~80%) of sulfonylurea usage seen in the type 2 diabetes mellitus study is similar to that expected in Canadian patients with type 2 diabetes mellitus.

While the study patients were not all using Lantus prior to study entry, a significant proportion were using Lantus (84% in the type 1 diabetes mellitus study, 40% in the type 2 diabetes mellitus study). According to the manuscript cited by the manufacturer by Hadjiyianni et al.,[4] there were "no statistically significant treatment differences observed for…change in HbA1c from baseline to the 24 week endpoint." Regarding dose initiating in these patients, the Basaglar product monograph states:

> "If transferring patients from Lantus to Basaglar, the dose of Basaglar should be the same as Lantus and the time of day for administration should be determined by the physician. A program of close metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting insulin analogue may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogues. Such patients may experience a greater insulin response to Basaglar. With improved metabolic control and resulting increase in insulin sensitivity, adjustment of the dose(s) of antidiabetic treatments may become necessary."

6. EXTRAPOLATION OF INDICATIONS

6.1 Manufacturer's Rationale for Extrapolation

Basaglar is indicated in the treatment of pediatric patients (older than six years of age) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. The use of Basaglar in pediatric (older than six years of age) type 1 diabetes mellitus is supported by the similar product quality characteristics of Basaglar and Lantus and by the similar pathophysiology of pediatric type 1 diabetes mellitus compared with the studied population (adult type 1 diabetes mellitus). In addition, comparative non-clinical, human pharmacokinetic, and clinical efficacy and safety studies have been conducted to demonstrate comparable clinical profiles between Basaglar and the reference product (Lantus) (Module 2.5. Section 2.5.6.1: Benefits and Risks, page 60-61).

6.2 Health Canada's Conclusion on Extrapolation

At the time this section was drafted by the manufacturer for the CADTH Common Drug Review (CDR) submission, the Biologics Safety and Efficacy Assessment Report is pending. However, Clarifax from July 20th (question # 15) indicated pending acceptance of a pediatric indication in patients older than six years of age *"pending the response to questions contained in this clinical clarifax as well as the completion of the review of the clinical PK/PD, safety and efficacy package and the C&M package."* The final product monograph,[ix] which includes the pediatric indication, supports the final acceptance of this rationale for extrapolation.

6.3 International Regulatory Conclusions on Extrapolation

6.3.1 European Medicines Agency

The approved European label included use of Abasaglar[x] (approved trade name in Europe; formerly known as Abasria) in pediatric patients older than two years of age based on established similarity to Lantus[xi] and based on three efficacy and safety studies of Lantus in pediatric patients:

- A randomized, controlled clinical study of pediatric patients (age range six to 15 years) with type 1 diabetes (n = 349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal.[xii]
- A crossover study comparing insulin glargine plus lispro insulin with NPH plus regular human insulin (each treatment administered for 16 weeks in random order) in 26 adolescent type 1 diabetic patients aged 12 to 18 years was also performed.[xiii]
- A 24-week parallel group study was conducted in 125 children with type 1 diabetes mellitus aged two to six years, comparing insulin glargine given once daily in the morning to NPH insulin given once or twice daily as basal insulin.[xiv]

6.3.2 US Food and Drug Administration

Basaglar was approved for use in the United States on December 16, 2015.

6.3.3 Australian Therapeutic Goods Administration

In the approved Australian label,[xv] Basaglar is indicated for use in the treatment of type 1 diabetes in children. Although there is no age restriction in the indication, it is noted in the label that insulin glargine has not been studied in children younger than two years of age. The main rationale for the extrapolation of indications is cited as:

"The ACPM noted that Lantus is registered for use in children from the age of 2 years but has not been studied in children less than 2 years of age. Therefore, as Abasria has been accepted as similar to Lantus, the ACPM advised that extrapolation can be allowed for use in children 2 years and older." [xvi]

6.4 CADTH Common Drug Review Comments on Extrapolation

An extrapolation was made to the pediatric type 1 diabetes mellitus indication (older than six years of age) and was based on the similarity between Basaglar and Lantus "in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and based on clinical experience with the reference products."[1]

The Health Canada Reviewer's Reports noted that the decision to extrapolate an indication is based on several principles:[11]

1. A demonstration of product similarity through a detailed and comprehensive comparative product characterization.
2. A thorough understanding of the mechanism(s) of action and the similarities and differences in the mechanism(s) of action that play a role in each of the indicated conditions for which a sponsor applies.
3. An understanding of the pathophysiological mechanism(s) of the indicated diseases and the differences and similarities between them.
4. Safety profile in the respective conditions and/or populations.
5. Clinical experience with the reference drug.

The comparison between a biosimilar and innovator product should be conducted in the most sensitive population, so that differences are more likely to be detected. The setting of adult healthy volunteers for glucose outcomes was considered adequate in this regard. Adults with type 1 diabetes mellitus was considered to be the most sensitive setting for detecting differences in immunogenicity.[11]

The Health Canada reviewers concluded, "While there are gaps in the understanding of the molecular mechanisms of action of insulins in general, it is not expected that the mechanisms responsible for their therapeutic effects differ significantly between adult and pediatric type 1 diabetes mellitus patients."[11] The European Medicines Agency allowed a slightly wider extrapolation to diabetic children aged two years and older.[12]

7. COST COMPARISON

Basaglar (both cartridges and KwikPens) is priced at a 15% discount to Lantus (cartridges and SoloSTAR) based on wholesale prices outside of Quebec. As dosing is titrated based on a patient's insulin resistance, there is no "standard" daily dose of either Basaglar or Lantus. A dose of 50 units per day was chosen for the example in Table 28.

TABLE 28: COST COMPARISON OF BASAGLAR AND LANTUS

Drug/ Comparator	Strength	Dosage Form	Price Per Unit of Insulin ($)	Recommended Dose	Average Drug Cost ($)
Basaglar	100 units/mL	Solution for injection (cartridge or KwikPen)	$0.0526 (Source: Data on file, Eli Lilly Canada Inc.)	Insulin-naive patients with type 2 diabetes: Start at a dose of 10 units once daily, and subsequently adjust according to the patient's need Switches from Lantus: The dose of Basaglar should be the same as Lantus (Source: Basaglar Product Monograph[xvii])	Based on 50 units/day $2.6307
Lantus	100 units/mL	Solution for injection (cartridge or SoloSTAR)	$0.0619 (Source: IMS-Brogan Delta PA: Ontario Wholesale [September 2015])	Insulin-naive patients with type 2 diabetes: Start at a dose of 10 U once daily, and subsequently adjust according to the patient's need (Source: Lantus Product Monograph[xviii])	Based on 50 units/day $3.0950

7.1 CDR Reviewer Comments Regarding Cost Information

7.1.1 Summary of Manufacturer's Analysis

Subsequent entry insulin glargine (Basaglar) is available as a 100 U/mL solution for injection with a reusable pen (cartridge) or a pre-filled pen (KwikPen) at a manufacturer-submitted price of $0.0526 per unit of insulin. The manufacturer submitted a cost comparison between Basaglar and reference insulin glargine (Lantus) for the two indications reviewed. Lantus is currently available as a 100 U/mL solution for use with a reusable pen (cartridge), a pre-filled pen, and a vial for use with a syringe, priced at $0.0619 per unit of insulin, according to the Ontario Drug Benefit (ODB) formulary (January 2016). Price per unit of insulin and daily cost for 50 units/day were compared by the manufacturer, as there is no "standard" dose of either Basaglar or Lantus because dosing is titrated based on patient response. Basaglar is priced 15% lower than Lantus per unit.

7.1.2 CADTH Common Drug Review Assessment of Manufacturer's Cost Comparison

- The methods used by the manufacturer for the cost comparison were found to be appropriate by CDR and the clinical expert involved in this review.
- CDR assessment included additional comparisons with other long-acting insulin analogues and intermediate-acting human insulin. The cost savings associated with Basaglar are greater when

compared with insulin detemir (35% to 36% more costly per unit than Basaglar) than Lantus (17% to 18% more costly per unit than Basaglar). However, insulin NPH is 43% to 57% less costly per unit than Basaglar.

TABLE 29: COST COMPARISON OF BASAGLAR WITH LONG-ACTING INSULIN ANALOGUES AND INTERMEDIATE-ACTING HUMAN INSULIN

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost Per Unit ($)	Cost Differential Per Unit ($) — for Comparator vs. Basaglar	% Difference Per Unit — for Comparator vs. Basaglar
Long-acting insulin analogues						
Insulin glargine (Basaglar)	**100 U/mL**	**5 × 3 mL cartridge** **5 × 3 mL disposable pen**	**78.90** **78.90**	**0.0526** **0.0526**	**Reference**	
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	92.85 92.85 61.69	0.0619 0.0619 0.0617	0.0093 0.0093 0.0091	17.7 17.7 17.3
Insulin detemir (Levemir)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	106.76 107.29	0.0712 0.0715	0.0186 0.0189	35.4 35.9
Intermediate-acting human insulin						
Insulin isophane (Humulin NPH)	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.12 22.99	0.0301 0.0230	–0.0225 –0.0296	–42.8 –56.3
Insulin isophane (Novolin ge NPH)	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.34 22.56	0.0296 0.0226	–0.0230 –0.0300	–43.7 –57.0

vs. = versus.
Source: Ontario Drug Benefit prices (accessed January 2016).[13]

7.1.3 Issues for Consideration

- Dosage of insulin glargine is based on patient response. Basaglar and Lantus were demonstrated to have similar pharmacokinetics, pharmacodynamics, clinical efficacy, and harms, and share the same dosing strategies; therefore, the relative cost difference between the drugs is likely to be maintained, regardless of patient characteristics or required daily dose.
- The clinical expert indicated that there are no anticipated issues with switching from Lantus to Basaglar.
- The listing criteria for Lantus differ across publicly funded drug plans in Canada, whereby Lantus is available as a full benefit in some jurisdictions and as a restricted benefit in others (Appendix 2: Drug Plan Listing Status for Reference Product). The expected savings from Basaglar compared with Lantus are based on the assumption that the listing criteria for Lantus would be applied to Basaglar.
- Should the actual cost of Lantus to drug plans differ from the list price used in the analysis, this could impact the cost differential and potential savings to the drug plans.

8. DISCUSSION

The Health Canada reviewers indicated, "Overall, the therapeutic benefits seen in the pivotal studies are comparable to the reference product, Lantus, and the benefits of Basaglar therapy are considered to outweigh the potential risks. Basaglar has an acceptable safety profile based on the non-clinical data and clinical studies. The identified safety issues can be managed through labelling, and adequate monitoring."[5]

Insulin glargine as Lantus has been available in Canada since 2002. Patient input received for this CDR submission indicated that some patients would like to have another insulin glargine product available if it was similar to Lantus and was less costly.

The data received by CDR for this review are an abbreviated form of the data reviewed by Health Canada. Based on the submitted data, the conclusion is reasonable that Basaglar and Lantus are similar with respect to clinical efficacy and harm in the populations for which it is indicated.

At the manufacturer's submitted confidential price, Basaglar is 15% less expensive than Lantus based on the ODB price of Lantus.

APPENDIX 1: ADDITIONAL DATA

FIGURE 1: 12-MONTH LONG-TERM STORAGE REVERSED-PHASE PURITY CHROMATOGRAMS[xix]

Figure 1 contained confidential information and was removed at the request of the manufacturer.

FIGURE 2: SIX-MONTH ACCELERATED REVERSED-PHASE PURITY CHROMATOGRAMS[xx]

Figure 2 contained confidential information and was removed at the request of the manufacturer.

FIGURE 3: LONG-TERM AND ACCELERATED IMPURITY RESULTS (%) FOR BASAGLAR INJECTION AND LANTUS STABILITY STUDIES[xxi]

Figure 3 contained confidential information and was removed at the request of the manufacturer.

FIGURE 4: OVERALL SUMMARY OF ADVERSE EVENTS (FULL ANALYSIS SET) — BASAGLAR ISS: I4L-MC-ABEB (52 WEEKS), I4L-MC-ABEC (24 WEEKS)[xxii]

Figure 4 contained confidential information and was removed at the request of the manufacturer.

TABLE 30: COMPARISON OF THE PRIMARY PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS OF BASAGLAR, EU-APPROVED, US-APPROVED LANTUS IN THREE TWO-TREATMENT, FOUR-PERIOD, CROSSOVER DESIGN STUDIES[xxiii]

Treatment (0.5 Units/kg)	N (n)	Geometric Mean (CV %)[a]	Ratio of LS Geometric Means (Test[b]/Reference) (90% CI)[c]
Statistical analysis of pharmacokinetic parameters			
$AUC_{[0–24]}$ (pmol h/L)			
LY IGlar[b]	87 (165)	1,720 (42)	0.90 (0.86 to 0.94)
US IGlar	89 (167)	1,900 (35)	
LY IGlar[b]	79 (156)	1,810 (40)	0.91 (0.87 to 0.96)
EU IGlar	80 (157)	1,980 (36)	
EU IGlar[b]	40 (75)	2,000 (35)	0.98 (0.91 to 1.05)
US IGlar	40 (76)	2,060 (39)	
C_{max} (pmol/L)			
LY IGlar[b]	88 (167)	103 (41)	0.92 (0.87 to 0.96)
US IGlar	89 (169)	111 (34)	
LY IGlar[b]	80 (158)	112 (39)	0.95 (0.90 to 1.00)
EU IGlar	80 (158)	119 (34)	
EU IGlar[b]	40 (76)	120 (33)	0.99 (0.92 to 1.06)
US IGlar	40 (77)	122 (37)	

Treatment (0.5 Units/kg)	N (n)	Geometric Mean (CV %)[a]	Ratio of LS Geometric Means (Test[b]/Reference) (90% CI)[c]
T_{max} (h)[d]			
LY IGlar[b]	88	12.00	0.50 (20.76 to 1.25)
US IGlar	89	12.00	
LY IGlar[b]	80	12.00	0.00 (20.75 to 0.75)
EU IGlar	80	13.50	
EU IGlar[b]	40	12.00	20.75 (21.50 to 0.50)
US IGlar	40	12.00	
Statistical analysis of pharmacodynamic parameters			
G_{tot} (mg/kg)			
LY IGlar[b]	88 (171)	1,670 (60)	0.91 (0.85 to 0.98)
US IGlar	88 (170)	1,820 (74)	
LY IGlar[b]	80 (158)	2,580 (45)	0.95 (0.91 to 1.00)
EU IGlar	80 (158)	2,710 (40)	
EU IGlar[b]	40 (76)	1,870 (84)	1.00 (0.89 to 1.13)
US IGlar	40 (77)	1,880 (77)	
R_{max} (mg/kg/min)			
LY IGlar[b]	88 (171)	2.12 (54)	0.93 (0.88 to 0.98)
US IGlar	88 (170)	2.27 (58)	
LY IGlar[b]	80 (158)	2.85 (46)	0.99 (0.94 to 1.04)
EU IGlar	80 (158)	2.88 (41)	
EU IGlar[b]	40 (76)	2.35 (67)	0.97 (0.88 to 1.07)
US IGlar	40 (77)	2.44 (63)	

AUC = area under the curve; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; EU = European Union; EU IGlar = EU-approved Lantus; G_{tot} = total glucose infusion over the clamp duration; LS = least squares; LY IGlar = Basaglar; n = number of observations; N = number of patients; R_{max} = maximum glucose infusion rate; T_{max} = time to maximum plasma concentration; US = United States; US IGlar = US-approved Lantus.

[a] Summary statistics of pharmacokinetic and pharmacodynamic parameters; does not reflect results of the statistical analysis.

[b] The test treatment in each comparison.

[c] Statistical model: log(parameter) = period + sequence + treatment + error, subject (random), period sequence treatment (categorical).

[d] Median or median difference (95% CI) are presented for T_{max}. T_{max} was analyzed using a nonparametric approach based on the Hodges-Lehmann method. Analysis was based on patient's T_{max} values averaged across the 2 occasions where the same treatment was administered, if applicable.

APPENDIX 2: DRUG PLAN LISTING STATUS FOR REFERENCE PRODUCT

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit)
UR	Under review
—	Information not available

TABLE 31: LISTING STATUS FOR LANTUS

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK[a]	NT[b]	NIHB	DND	VAC
Adults with type 1 or 2 diabetes	RES	FB	FB	RES	FB	RES	RES	RES	RES	RES	FB	FB	—	—
Pediatric (> 6 years) with type 1 diabetes	RES	FB	FB	RES	FB	RES	RES	RES	RES	NB	FB	FB	—	—

AB = Alberta, BC = British Columbia, CDR = CADTH Common Drug Review; DND = Department of National Defence; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] Source for YK: Online formulary accessed at: http://apps.gov.yk.ca/drugs/f?p=161:9000:3061560371925832:SEARCH:NO:::&cs=353B44F53CCAE7357F1120E41A7123F80
All others sourced from IMS-Brogan. iMAM.

[b] Source for NT: Canadian Diabetes Association. Formulary Listings for Diabetes Medications in Canada. 26 August 2015. Accessed online at: www.diabetes.ca/getmedia/c614895c-d849-44c4-bd4a-5befa4cf9d9c/pt-formulary-listing-aug-26-2015.pdf.aspx

TABLE 32: RESTRICTED BENEFIT CRITERIA FOR LANTUS FOR THE TREATMENT OF ADULTS OR PEDIATRIC PATIENTS WITH TYPE 1 OR 2 DIABETES

Drug Plan	Criteria for Restricted Benefit
BC	**Type 1 Diabetes — Patient of Any Age** Patient has a diagnosis of type 1 diabetes requiring insulin and is currently taking insulin NPH and/or pre-mix insulin daily at optimal dosing AND: 1. Has experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management OR 2. Has experienced or continues to experience severe, systemic, or local allergic reaction to existing insulin treatment **Type 2 Diabetes** — Patient older than 17 years of age only Patient has a diagnosis of type 2 diabetes requiring insulin and is currently taking insulin NPH and/or pre-mix insulin daily at optimal dosing AND: 3. Has experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management OR 4. Has experienced or continues to experience severe, systemic or local allergic reaction to existing insulin treatment **Practitioner Exemptions** Practitioners in the following specialty are not required to submit a Special Authority Request form for coverage: Endocrinology. **Special Notes** • Specialists with experience in pediatric diabetes management may also have prescriptions covered for patients who meet the coverage criteria but are required to submit a Special Authority request. • For patients who have experienced or continue to experience severe, systemic or local allergic reaction to existing insulin treatment, documentation of previous trials (i.e., specific insulin tried and patient's response) is required.
MB	As a first-line alternative, secondary to NPH and/or pre-mix at daily optimal dose, for patients who have been diagnosed with type 1 or type 2 diabetes AND who have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management OR have documented severe or continuing systemic or local allergic reaction to existing insulin.
NB	For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND: • have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND • have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management • OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).
NS	For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND: • have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND • have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management • OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).
PE	For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND: • have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND • have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management • OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).

Drug Plan	Criteria for Restricted Benefit
NL	For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND: • have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND • have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management • OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).
YK	Adults diagnosed with type 1 or type 2 diabetes requiring insulin and are currently taking insulin NPH and/or pre-mix insulin at optimal dosing AND: • have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management OR • have documented severe or continuing allergic reaction to existing insulin (full documentation required). Must be prescribed by an endocrinologist or visiting internal medicine specialist. Specialists consult to be provided.

APPENDIX 3: SUMMARY OF PATIENT INPUT

1. Brief Description of Patient Groups Supplying Input

The Canadian Diabetes Association (CDA) and the Consumer Advocare Network (CAN) provided a combined submission and declared no conflict of interest in its preparation.

The CDA provides education and services, advocates on behalf of people with diabetes, supports research, and translates research into practical applications. The CDA is supported in its efforts by a community-based network of volunteers, employees, health care professionals, researchers, and partners. The CDA solicits and receives unrestricted educational grants from multiple manufacturers and vendors of medications, supplies, and devices for diabetes and its complications. These funds are used to help the CDA support community programs and services for people with diabetes and to fund research and advocacy across Canada.

The CAN is a registered not-for-profit organization that provides education and support to patient groups to promote engagement in health care policy and decision-making. The CAN has received unrestricted educational grants over the past five years to develop materials and workshops on subsequent entry biologics (SEBs) from BIOTECanada, Janssen-Ortho, Amgen, Sanofi, and Wyatt Health Management, as well as funding support from Health Canada to participate in workshops and consultations on SEBs.

2. Condition-Related Information

The CDA solicited patient input through surveys distributed through social media and email. The data for this submission came from an online survey of Canadians with diabetes (October 2015). Respondents included 367 patients with type 1 or type 2 diabetes and 61 caregivers.

Diabetes is a chronic and progressive disease. Type 1 diabetes occurs when the body does not produce insulin or produces very little insulin. Type 2 diabetes occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced. Common symptoms of diabetes include fatigue, thirst, and weight change. High blood glucose levels can cause long-term complications such as blindness, heart disease, kidney problems, nerve damage, and erectile dysfunction.

The majority of respondents indicated that diabetes has limited activities and opportunities including travel and career. Many are frustrated that they cannot lead a “normal life” due to diabetes. Some reported that they have lost driving privileges, employment, independence, and spontaneity in daily life in general. It is also challenging when a person needs to manage diabetes as well as other co-existing conditions. One respondent replied, “You give up a lot of control in your life to your diabetes… Following your dreams and choosing a career path, travelling, playing sports — those are all seriously shadowed by the question will I have enough supplies; will my numbers be good enough to do this?” There was also a frequent emphasis on the psychological and emotional impact of diabetes on the lives of respondents as well as their family members, as a result of the need to adjust to changes in diet and lifestyle, stress and anxiety about hypoglycemia, daily medication and treatment management, strain on relationships with family, and financial burden.

3. Current Therapy-Related Information

In the survey, 255 patients had experience with Lantus. The majority of respondents did not have concerns with accessing long-acting insulins, but some respondents had experienced shortage of Lantus supply at pharmacies. Some patients expressed that switching to Lantus from NPH insulin had resulted in fewer injections and better glucose control. Other patients expressed a desire to reduce the number of injections further, combine insulins (e.g., Lantus and Humalog) into one injection device, and achieve better blood glucose control. Some patients expressed discontent with the requirement of some jurisdictions that nocturnal hypoglycemia on NPH insulin be documented before Lantus is covered by the drug plan. A total of 17% of survey respondents said that they have experienced difficulty accessing Lantus because of the cost of the product.

4. Expectations About the Drug Being Reviewed

Only two respondents to the survey had used Basaglar. Respondents who have experience with Lantus would like to see that Basaglar is at least as effective as Lantus, available at a reduced cost (or covered under a drug plan), have a longer duration of action compared with Lantus, and have a reduced incidence of adverse effects (e.g., burning sensation, allergic reactions such as itchy hives or hypoglycemic reactions). Respondents hope that Basaglar would help fill the gap of any shortages that may occur with Lantus.

There was some concern expressed regarding the quality of SEBs, with some respondents saying other SEBs may not possess the same quality as the reference drug. Most patients expressed uneasiness about switching from Lantus to Basaglar and vice versa. While some appeared to be more confident about the similarities between these two drugs (“If it works exactly the same with the same required units, then it should be interchangeable without physician approval”), others were more cautious as to whether these two drugs are the same (“My understanding is that these drugs would be similar but not the same. As such, they shouldn't be taken interchangeably.”)

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