



# Common Drug Review

## *Subsequent Entry Biologic Review Report*

November 2016

|                        |                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Drug</b>            | Insulin glargine (rDNA origin) injection (Basaglar)                                                                                                                                                                                                                                                                                                                                   |
| <b>Indications</b>     | <ol style="list-style-type: none"><li>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.</li><li>2. Treatment of pediatric patients (&gt; 6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.</li></ol> |
| <b>Listing request</b> | List in accordance to the Health Canada-approved indications                                                                                                                                                                                                                                                                                                                          |
| <b>Dosage form(s)</b>  | Solution for injection 100 U/mL                                                                                                                                                                                                                                                                                                                                                       |
| <b>NOC date</b>        | September 1, 2015                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Manufacturer</b>    | 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.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

You are permitted to make copies of this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH. You may not otherwise copy, modify, translate, post on a website, store electronically, republish, or redistribute any material from this document in any form or by any means without the prior written permission of CADTH.

Please contact CADTH's Vice-President of Corporate Services at [corporateservices@cadth.ca](mailto:corporateservices@cadth.ca) with any inquiries about this notice or other legal matters relating to CADTH's services.

## TABLE OF CONTENTS

|                                                                  |    |
|------------------------------------------------------------------|----|
| ABBREVIATIONS .....                                              | IV |
| EXECUTIVE SUMMARY .....                                          | V  |
| 1. PRODUCT INFORMATION .....                                     | 1  |
| 1.1 Overview of the Subsequent Entry Biologic Product .....      | 1  |
| 1.2 Overview of Lantus (Reference Product).....                  | 2  |
| 2. INDICATIONS.....                                              | 3  |
| 2.1 Health Canada–Approved Indications .....                     | 3  |
| 2.2 Proposed Indications Under Review by Health Canada .....     | 3  |
| 3. MANUFACTURER’S REQUESTED LISTING CRITERIA .....               | 4  |
| 3.1 Requested Listing Criteria.....                              | 4  |
| 3.2 Rationale for Requested Listing Criteria .....               | 4  |
| 4. BIOSIMILARITY .....                                           | 5  |
| 4.1 Quality Information .....                                    | 5  |
| 4.2 Pivotal Clinical Studies .....                               | 6  |
| 4.3 Pharmacokinetics .....                                       | 28 |
| 4.4 Immunogenicity .....                                         | 28 |
| 5. CRITICAL APPRAISAL OF CLINICAL STUDIES .....                  | 29 |
| 5.1 Internal Validity .....                                      | 29 |
| 5.2 External Validity.....                                       | 32 |
| 6. EXTRAPOLATION OF INDICATIONS .....                            | 33 |
| 6.1 Manufacturer’s Rationale for Extrapolation.....              | 33 |
| 6.2 Health Canada’s Conclusion on Extrapolation.....             | 33 |
| 6.3 International Regulatory Conclusions on Extrapolation.....   | 33 |
| 6.4 CADTH Common Drug Review Comments on Extrapolation.....      | 34 |
| 7. COST COMPARISON .....                                         | 35 |
| 7.1 CDR Reviewer Comments Regarding Cost Information .....       | 35 |
| 8. DISCUSSION .....                                              | 37 |
| APPENDIX 1: ADDITIONAL DATA .....                                | 38 |
| APPENDIX 2: DRUG PLAN LISTING STATUS FOR REFERENCE PRODUCT ..... | 40 |
| APPENDIX 3: SUMMARY OF PATIENT INPUT .....                       | 43 |
| REFERENCES.....                                                  | 45 |

**Tables**

|                                                                                                                                                                                                          |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 1: Subsequent Entry Biologic Overview.....                                                                                                                                                         | 1  |
| Table 2: Requested Listing Criteria for Indications to be Reviewed by the CADTH<br>Common Drug Review .....                                                                                              | 4  |
| Table 3: Comparative Testing Results .....                                                                                                                                                               | 5  |
| Table 4: Pivotal Pharmacokinetic/Pharmacodynamic Study.....                                                                                                                                              | 6  |
| Table 5: Pivotal Phase 3 Studies .....                                                                                                                                                                   | 7  |
| Table 6: Study Characteristics — ABEO .....                                                                                                                                                              | 7  |
| Table 7: Study Characteristics — ELEMENT 1.....                                                                                                                                                          | 10 |
| Table 8: Summary of Statistical Analyses in the ELEMENT 1 Trial.....                                                                                                                                     | 13 |
| Table 9: Baseline Patient Demographics and Patient Characteristics for the ELEMENT 1 Trial.....                                                                                                          | 13 |
| Table 10: Summary of Patient Disposition for ELEMENT 1 (ABEB).....                                                                                                                                       | 14 |
| Table 11: Summary of A1C Change in ELEMENT 1 (Per-Protocol).....                                                                                                                                         | 15 |
| Table 12: Summary of Daily Insulin Dose Change in ELEMENT 1 .....                                                                                                                                        | 16 |
| Table 13: Selected Patient-Reported Outcomes in ELEMENT 1 .....                                                                                                                                          | 16 |
| Table 14: Study Characteristics — ELEMENT 2 .....                                                                                                                                                        | 18 |
| Table 15: Summary of Statistical Analyses in the ELEMENT 2 (ABEC) Study.....                                                                                                                             | 21 |
| Table 16: Baseline Patient Demographics and Patient Characteristics for the ELEMENT 2 Trial .....                                                                                                        | 21 |
| Table 17: Summary of Patient Disposition for ELEMENT 2 (ABEC).....                                                                                                                                       | 22 |
| Table 18: Change in A1C From Baseline to End Point in ELEMENT 2.....                                                                                                                                     | 22 |
| Table 19: Summary of A1C Change in ELEMENT 2 (Per-Protocol).....                                                                                                                                         | 23 |
| Table 20: Summary of Daily Insulin Dose Change in ELEMENT 2 .....                                                                                                                                        | 24 |
| Table 21: Selected Patient-Reported Outcomes in ELEMENT 2 .....                                                                                                                                          | 24 |
| Table 22: Basal Insulin Dose — Change From Baseline to End Point (Last Observation<br>Carried Forward) by Entry Basal Insulin Treatment (ELEMENT 2).....                                                 | 24 |
| Table 23: Overview of Treatment-Emergent Adverse Events in ELEMENT 1 and ELEMENT 2 .....                                                                                                                 | 25 |
| Table 24: Most Clinically Relevant Hypoglycemia Events — ELEMENT 1 (52 Weeks),<br>Full Analysis Set .....                                                                                                | 26 |
| Table 25: Most Clinically Relevant Hypoglycemia Events — ELEMENT 2 (24 Weeks),<br>Full Analysis Set .....                                                                                                | 26 |
| Table 26: Summary of Pharmacokinetics From Pivotal ABEO Trial .....                                                                                                                                      | 28 |
| Table 27: Overview of Basaglar Studies <sup>6</sup> .....                                                                                                                                                | 29 |
| Table 28: Cost Comparison of Basaglar and Lantus.....                                                                                                                                                    | 35 |
| Table 29: Cost Comparison of Basaglar With Long-Acting Insulin Analogues and<br>Intermediate-Acting Human Insulin .....                                                                                  | 36 |
| Table 30: Comparison of the Primary Pharmacokinetic and Pharmacodynamic Parameters<br>of Basaglar, EU-Approved, US-Approved Lantus in Three Two-Treatment, Four-Period,<br>Crossover Design Studies..... | 38 |
| Table 31: Listing Status for Lantus .....                                                                                                                                                                | 40 |
| Table 32: Restricted Benefit Criteria for Lantus for the Treatment of Adults or Pediatric Patients<br>With Type 1 or 2 Diabetes .....                                                                    | 41 |

**Figures**

|                                                                                                                                         |    |
|-----------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 1: 12-Month Long-Term Storage Reversed-Phase Purity Chromatograms.....                                                           | 38 |
| Figure 2: Six-Month Accelerated Reversed-Phase Purity Chromatograms.....                                                                | 38 |
| Figure 3: Long-Term and Accelerated Impurity Results (%) for Basaglar Injection and Lantus<br>Stability Studies .....                   | 38 |
| Figure 4: Overall Summary of Adverse Events (Full Analysis Set) — Basaglar ISS: I4L-MC-ABEB<br>(52 Weeks), I4L-MC-ABEC (24 Weeks) ..... | 38 |

## **ABBREVIATIONS**

|                        |                                                |
|------------------------|------------------------------------------------|
| <b>A1C</b>             | glycated hemoglobin                            |
| <b>ALBSS</b>           | Adult Low Blood Sugar Survey                   |
| <b>AE</b>              | adverse event                                  |
| <b>ANCOVA</b>          | analysis of covariance                         |
| <b>AUC</b>             | area under the curve                           |
| <b>BG</b>              | blood glucose                                  |
| <b>CAN</b>             | Consumer Advocare Network                      |
| <b>CDA</b>             | Canadian Diabetes Association                  |
| <b>CDR</b>             | CADTH Common Drug Review                       |
| <b>CI</b>              | confidence interval                            |
| <b>C<sub>max</sub></b> | maximum plasma concentration                   |
| <b>CMH</b>             | Cochran–Mantel–Haenszel                        |
| <b>CSR</b>             | Clinical Study Report                          |
| <b>CTD</b>             | Common Technical Document                      |
| <b>DB</b>              | double-blind                                   |
| <b>FAS</b>             | full analysis set                              |
| <b>FBG</b>             | fasting blood glucose                          |
| <b>GIR</b>             | glucose infusion rate                          |
| <b>G<sub>tot</sub></b> | total glucose infusion over the clamp duration |
| <b>ITSQ</b>            | Insulin Treatment Satisfaction Questionnaire   |
| <b>ITT</b>             | intention-to-treat                             |
| <b>LOCF</b>            | last observation carried forward               |
| <b>LS</b>              | least squares                                  |
| <b>ODB</b>             | Ontario Drug Benefit                           |
| <b>PD</b>              | pharmacodynamic                                |
| <b>PK</b>              | pharmacokinetic                                |
| <b>R<sub>Max</sub></b> | maximum glucose infusion rate                  |
| <b>SAE</b>             | serious adverse event                          |
| <b>SE</b>              | standard error                                 |
| <b>SEB</b>             | subsequent entry biologic                      |
| <b>SD</b>              | standard deviation                             |
| <b>SMBG</b>            | self-monitoring of blood glucose               |
| <b>TEAE</b>            | treatment-emergent adverse event               |
| <b>TEAR</b>            | treatment-emergent antibody response           |
| <b>WDAE</b>            | 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.”<sup>1</sup>

### **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)<br>02444852 (pre-filled pen)                                                                      | 02251930 (cartridge)<br>02294338 (pre-filled pen)<br>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<br><br>Hydrochloric acid and sodium hydroxide for pH adjustment | Glycerol 85%, m-Cresol, polysorbate 20 (10 mL vial only), zinc, and water for injection.<br><br>Hydrochloric acid and sodium hydroxide for pH adjustment |
| Impurities <sup>a</sup>       | [REDACTED]                                                                                                             | —                                                                                                                                                        |

<sup>a</sup> 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.<sup>i</sup>

### 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

(see Figure 1, Appendix 1: Additional Data).

ii

(see Figure 2, Appendix 1: Additional Data).

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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>The manufacturer requests that Basaglar be listed in accordance to the Health Canada–approved indications:</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• In the treatment of pediatric patients (&gt; 6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.</li> </ul> |

#### 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

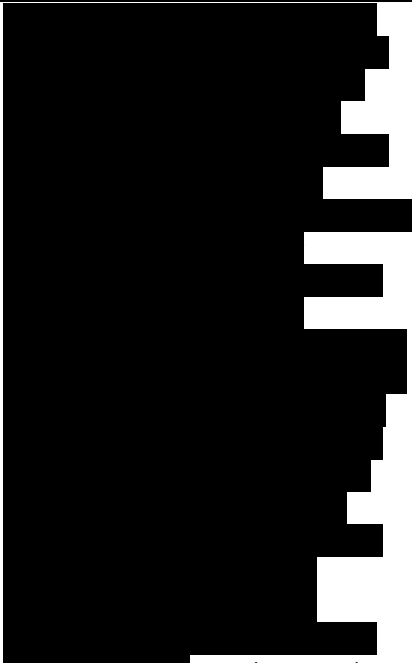
### 4.1 Quality Information

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 ( $\leq 0.007\%$ 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 |

## CDR SUBSEQUENT ENTRY BIOLOGIC REVIEW REPORT FOR BASAGLAR

| 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      |                                                                                                                                                | <br>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 <sup>iv</sup> | 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 <sup>v</sup><br>(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 <sup>vi</sup><br>(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-naïve, 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<sup>vii</sup>

(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<br>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 | <ul style="list-style-type: none"> <li>Overtly healthy men or women aged 21 to 65 years</li> <li>BMI between 18.5 and 29.9 kg/m<sup>2</sup></li> <li>Fasting plasma glucose value &lt; 108 mg/dL (6.0 mmol/L)</li> </ul>                                     |
|                  | Exclusion criteria | <ul style="list-style-type: none"> <li>Known allergies to insulin or its excipients</li> <li>Major medical issues capable of altering the absorption, metabolism, or elimination or drugs, or of constituting a risk when taking study medication</li> </ul> |

| Characteristics |                             | Details for ABE0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DRUGS           | <b>Intervention</b>         | On 4 separate occasions, fasted patients received a single SC 0.5 U/kg dose of Basaglar or Lantus according to the following sequences:<br><ul style="list-style-type: none"> <li>• Basaglar – Lantus – Basaglar – Lantus</li> <li>OR</li> <li>• Lantus – Basaglar – Lantus – Basaglar</li> </ul> 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. |
|                 | <b>Comparator(s)</b>        | US Lantus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| DURATION        | <b>Run-in</b>               | There was a 6-week screening period before the first clamp                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                 | <b>Treatment</b>            | Single injection of study drug + 24-hour euglycemic clamp procedure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                 | <b>Follow-up</b>            | Patients were followed for 5 to 14 days after the fourth clamp procedure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| OUTCOMES        | <b>Primary end Point(s)</b> | 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                 | <b>Other end points</b>     | 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           | <b>Publications</b>         | 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. <i>Diabetes Care</i> ; 2015 Aug 25(online).<br><br>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  $\pm 5\%$  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- $\infty$ ). 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 ( $\pm$  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 | <ul style="list-style-type: none"> <li>Aged at least 18 years at screening</li> <li>Diagnosis of T1DM based on WHO diagnostic criteria</li> <li>Duration of diabetes of at least 1 year at screening</li> <li>A1C of <math>\leq 11.0\%</math></li> <li>Basal-bolus insulin therapy for at least 1 year prior to screening</li> <li>BMI of <math>\leq 35 \text{ kg/m}^2</math></li> </ul> |

## CDR SUBSEQUENT ENTRY BIOLOGIC REVIEW REPORT FOR BASAGLAR

| Characteristics |                                                             | Details for ELEMENT 1 (ABEB)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DRUGS           | <b>Exclusion criteria (list only major/select criteria)</b> | <ul style="list-style-type: none"> <li>• Prior exposure to a biosimilar insulin glargine</li> <li>• Excessive insulin resistance at study entry (total daily insulin dose <math>\geq 1.5</math> U/kg)</li> <li>• &gt; 1 episode of severe hypoglycemia within 6 months of screening</li> <li>• Use of oral antidiabetes medications or received treatment with pramlintide or CSII in the 3 months prior to screening</li> <li>• Use of twice-daily insulin glargine in the 6 months prior to screening</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                 | <b>Intervention</b>                                         | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                 | <b>Comparator(s)</b>                                        | Once-daily subcutaneous Lantus (dose equivalent to pre-study basal insulin)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| DURATION        | <b>Run-in</b>                                               | 2 weeks ( $\pm 1$ week)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                 | <b>Treatment</b>                                            | 24-week treatment followed by 28-week extension period                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                 | <b>Follow-up</b>                                            | 4 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| OUTCOMES        | <b>Primary end point(s)</b>                                 | 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%.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                 | <b>Other end points</b>                                     | <p>A key secondary treatment comparison was to compare Lantus insulin glargine versus Basaglar at the non-inferiority margin of -0.4%.</p> <p>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 &lt; 7% and <math>\leq 6.5\%</math>, 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.</p> <p>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 <math>\geq 1\%</math> in insulin levels (measured by % binding) and <math>\geq 30\%</math> 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.</p> |
| NOTES           | <b>Publications</b>                                         | <p>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. <i>Diabetes, Obesity and Metabolism</i>. 2015Aug;17(8):726-733.</p> <ul style="list-style-type: none"> <li>• The clinicaltrials.gov identification code: NCT: 01421147</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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  $\geq 1\%$  in insulin levels (measured by % binding) and  $\geq 30\%$  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.<sup>2</sup>

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 =  $100 \times [(7 - \text{raw score})/6]$ . Higher scores indicate better treatment satisfaction.<sup>3</sup>

**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<br>n = 268 | Lantus<br>n = 267 |
|----------------------------------------|---------------------|-------------------|
| Mean (SD) age (years)                  | 41.0 (13.7)         | 41.4 (13.3)       |
| Male, n (%)                            | 155 (57.8)          | 155 (58.1)        |
| <b>Race, n (%)</b>                     |                     |                   |
| 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)       |

## CDR SUBSEQUENT ENTRY BIOLOGIC REVIEW REPORT FOR BASAGLAR

| Baseline Characteristic               | Basaglar<br>n = 268 | Lantus<br>n = 267 |
|---------------------------------------|---------------------|-------------------|
| Mean (SD) A1C, %                      | 7.8 (1.1)           | 7.8 (1.0)         |
| A1C < 7%, n (%)                       | 73 (27.2)           | 49 (18.4)         |
| <b>Time of basal injection, n (%)</b> |                     |                   |
| 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       |          |
| <b>At 24 weeks:</b>           |           |          |
| 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)  |
| <b>At 52 weeks:</b>           |           |          |
| 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) (%) | $\Delta$ BL to EP (LOCF) (%)     | EP (LOCF) (%) | $\Delta$ BL to EP (LOCF) (%)     |
| <b>Basaglar</b>       |               |                           |                                  |               |                                  |
| n <sup>a</sup>        | 251           | 251                       | 251                              | 251           | 251                              |
| LS mean               | 7.752         | 7.390                     | $-0.373^b$                       | 7.484         | $-0.279^b$                       |
| <b>Lantus</b>         |               |                           |                                  |               |                                  |
| n <sup>a</sup>        | 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<br>( $-0.012$ to $0.211$ ) |               | 0.005<br>( $-0.117$ to $0.127$ ) |

A1C = glycated hemoglobin; LOCF = last observation carried forward; LS = least squares.

<sup>a</sup> Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.

<sup>b</sup> 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  $\leq 6.5\%$  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  $\leq 6.5\%$  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)<br>N = 535 |                   | ELEMENT 1 (52-wk)<br>N = 534 |                   |
|-------------------------------------------|------------------------------|-------------------|------------------------------|-------------------|
|                                           | Basaglar<br>N = 268          | Lantus<br>N = 267 | Basaglar<br>N = 268          | Lantus<br>N = 267 |
| <b>Basal Insulin Dose (U/day)</b>         |                              |                   |                              |                   |
| No. of patients <sup>a</sup>              | 268                          | 266               | 268                          | 266               |
| Mean baseline                             | 25.1                         | 23.3              | 25.1                         | 23.3              |
| LS mean change from baseline <sup>b</sup> | 2.0                          | 2.0               | 2.7                          | 2.4               |
| <b>Total Insulin Dose (U/day)</b>         |                              |                   |                              |                   |
| No. of patients <sup>a</sup>              | 264                          | 266               | 264                          | 266               |
| Mean baseline <sup>b</sup>                | 55.5                         | 52.8              | 55.5                         | 52.8              |
| LS mean change from baseline              | 0.7                          | 0.6               | 2.9                          | 2.9               |

LS = least squares.

<sup>a</sup> Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.

<sup>b</sup> 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<br>(N = 268) | Lantus<br>(N = 267) | Statistical<br>Comparison |
|----------------------------------------------------|-----------------------|---------------------|---------------------------|
| ALBSS Behaviour – 24 weeks (LOCF)<br>(n = 255,257) | 12.73 (0.66)          | 12.53 (0.66)        | $P = 0.778$               |
| ALBSS Worry – 24 weeks (LOCF)<br>(n = 255,258)     | 15.39 (1.08)          | 14.27 (1.08)        | $P = 0.323$               |
| ITSQ Total – 24 weeks (LOCF)<br>(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:  $1.81 \pm 0.42$ ; Lantus:  $0.41 \pm 0.39$ ;  $P = 0.035$ ).

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

### **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  $\geq 1$  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 TEAEs. 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-TEAE 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 TEAEs 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-naïve

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     | <b>Objective</b>                   | Pivotal efficacy and safety study in adult patients with T2DM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                  | <b>Blinding</b>                    | Double-blind                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                  | <b>Study period</b>                | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                  | <b>Study centres</b>               | <b>Countries (no. investigators):</b> 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)                                                                                                                                                                                                                                                                                                                                                                 |
|                  | <b>Design</b>                      | Prospective, randomized, multinational, multi-centre, two-arm, active-controlled, double-blind, parallel-designed, non-inferiority study                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| STUDY POPULATION | <b>Randomized (N)</b>              | N = 759                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                  | <b>Inclusion criteria</b>          | <ul style="list-style-type: none"> <li>• ≥ 18 years old at screening</li> <li>• Diagnosis of T2DM based on WHO diagnostic criteria</li> <li>• Receipt of ≥ 2 OADs at stable doses for 12 weeks prior to screening, with or without insulin glargine, in accordance with local product labels</li> <li>• A1C ≥ 7.0% and ≤ 11.0% if insulin-naïve and A1C ≤ 11.0% if previously on insulin glargine</li> <li>• BMI ≤ 45 kg/m<sup>2</sup></li> </ul>                                                                                                                                           |
|                  | <b>Exclusion criteria</b>          | <ul style="list-style-type: none"> <li>• Use of any other insulin except insulin glargine in the previous 30 days</li> <li>• Exposure to a biosimilar insulin glargine in the previous 90 days</li> <li>• History of basal-bolus therapy, or requirement for mealtime insulin to achieve target glycemic control</li> <li>• Use of GLP-1 agonist in the previous 90 days</li> <li>• Use of pramlintide in the previous 90 days</li> <li>• Excessive insulin resistance (total insulin dose ≥ 1.5 U/kg)</li> <li>• &gt; 1 episode of severe hypoglycemia in the previous 6 months</li> </ul> |
| DRUGS            | <b>Intervention and Comparator</b> | Basaglar administered subcutaneously once daily, in combination with OADs (n = 376) vs. Lantus administered subcutaneously once daily, in combination with OADs (n = 380)                                                                                                                                                                                                                                                                                                                                                                                                                   |
| DURATION         | <b>Run-in</b>                      | 2 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                  | <b>Treatment</b>                   | 24 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                  | <b>Follow-up</b>                   | 4 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| OUTCOMES         | <b>Primary end point(s)</b>        | 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%.                                                                                                                                                                                                                                                                                                                                                                       |
|                  | <b>Other end points</b>            | <p>A key secondary treatment comparison was to compare Lantus insulin glargine vs. Basaglar at the non-inferiority margin of -0.4%.</p> <p>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 &lt; 7% and ≤ 6.5%, basal insulin dose at end point, and body weight. Pre-specified PRO measures were the ITSQ and ALBSS.</p>                                                                                     |

| 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           | <b>Publications</b> | 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-naïve 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.<br><ul style="list-style-type: none"> <li>clinicaltrials.gov identification code: NCT: 01421459</li> </ul> |

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-naïve 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  $\leq$  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  $\leq 6.5\%$ , 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 Type I 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<sup>2</sup> versus ≥ 25 kg/m<sup>2</sup> and < 30 kg/m<sup>2</sup> versus ≥ 30 kg/m<sup>2</sup>), 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<br>n = 376 | Lantus<br>n = 380 |
|----------------------------------------|---------------------|-------------------|
| Mean (SD) age (years)                  | 59.0 (10.2)         | 58.7 (10.0)       |
| Male, n (%)                            | 179 (47.6)          | 199 (52.4)        |
| <b>Race, n (%)</b>                     |                     |                   |
| 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)         |
| <b>Time of basal injection, n (%)</b>  |                     |                   |
| Daytime                                | 187 (49.7)          | 188 (49.5)        |
| Evening/bedtime                        | 189 (50.3)          | 192 (50.5)        |
| <b>Use of sulfonylurea, n (%)</b>      |                     |                   |
| 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 <sup>a</sup>        | 314           | 314                       | 314                     |
| LS mean               | 8.351         | 7.018                     | −0.1332 <sup>b</sup>    |
| Lantus                |               |                           |                         |
| n <sup>a</sup>        | 308           | 308                       | 308                     |
| LS mean               | 8.348         | 6.902                     | −1.448 <sup>b</sup>     |
| 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.

<sup>a</sup> Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.

<sup>b</sup> 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)<br>N = 756 |                  |
|-------------------------------------------|--------------------------------|------------------|
|                                           | Basaglar (N = 376)             | Lantus (N = 380) |
| <b>Basal insulin dose (U/day)</b>         |                                |                  |
| No. of patients <sup>a</sup>              | 374                            | 379              |
| Mean baseline                             | 15.4                           | 12.0             |
| LS mean change from baseline <sup>b</sup> | 32.3                           | 32.6             |
| <b>Total insulin dose (U/day)</b>         |                                |                  |
| # of patients <sup>a</sup>                | NA                             | NA               |
| Mean baseline                             | NA                             | NA               |
| LS mean change from baseline <sup>b</sup> | NA                             | NA               |

LS = least squares; NA = not available.

<sup>a</sup> Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.

<sup>b</sup> 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<br>(N = 376) | Lantus<br>(N = 380) | Statistical<br>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<br>LS Mean (SE) | N      | Δ From Baseline LS Mean<br>(SE) |         |
| Basal insulin dose (U/day) |          |                                 |        |                                 |         |
| Pre-study Lantus           | 154      | 20.25 (3.12)                    | 144    | 15.58 (3.20)                    | 0.171   |
| Insulin-naïve              | 220      | 39.76 (2.79)                    | 235    | 41.78 (2.72)                    |         |

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  $\leq 70$  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 TEAE, 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 TEAE.

#### 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 <sup>a</sup> | ELEMENT 1 (ABEB)<br>(52 Weeks) |                          | ELEMENT 2 (ABEC)<br>(24 Weeks) |                          |
|------------------------------------------------|--------------------------------|--------------------------|--------------------------------|--------------------------|
|                                                | Basaglar,<br>n (%) n = 268     | Lantus, n (%)<br>N = 267 | Basaglar,<br>n (%) n = 376     | Lantus, n (%)<br>n = 380 |
| Patients with $\geq 1$ 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 <sup>b</sup>                      | 13 (4.9)                       | 12 (4.5)                 | —                              | —                        |
| Diarrhea                                       | 12 (4.5)                       | 10 (3.7)                 | 9 (2.4)                        | 14 (3.7)                 |
| Hypertension <sup>b</sup>                      | 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.

<sup>a</sup> Occurring in  $> 3\%$  patients in either treatment group.

<sup>b</sup> 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  $\leq 3.9$  mmol/L (70 mg/dL), asymptomatic hypoglycemia with BG  $\leq 3.9$  mmol/L (70 mg/dL), probable symptomatic hypoglycemia, or unspecified hypoglycemia with BG  $\leq 3.9$  mmol/L (70 mg/dL).

**Severe hypoglycemia:** Symptoms requiring assistance of another person, including severe hypoglycemia events with BG  $\leq 3.9$  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  $\leq 70$  mg/dL (3.9 mmol/L).

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

|                                     | Basaglar<br>N = 268 |        | Lantus<br>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 |                     |        |                   |        |         |

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

|                                     | Basaglar<br>N = 376 |        | Lantus<br>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 |                     |        |                   |        |         |

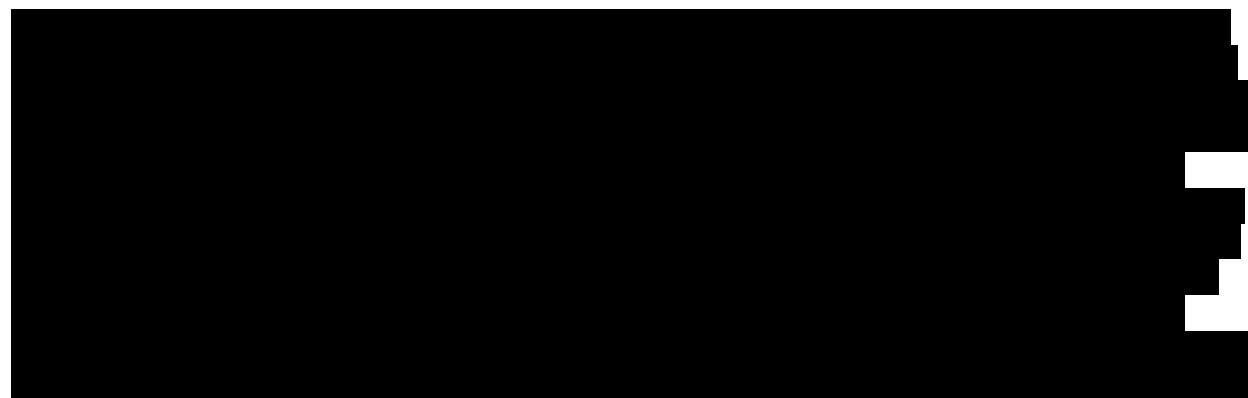
NR = not reported.

#### 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.



**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 <sup>a</sup>      | 1,715.51                          | 1,907.09                           | 0.9 (0.85 to 0.95)                         |
| C <sub>max</sub> pmol/L <sup>a</sup> | 102.91                            | 112.19                             | 0.92 (0.87 to 0.97)                        |
| T <sub>max</sub> (h) <sup>b</sup>    | 12.0                              | 12.0                               | NA                                         |
| T1/2 (h) <sup>b</sup>                | 10.0                              | 11.6                               | NA                                         |
| Bioavailability                      | Not assessed in ABEO              |                                    |                                            |
| Degradation                          | Not assessed in ABEO              |                                    |                                            |

AUC = area under the curve; CI = confidence interval; C<sub>max</sub> = maximum concentration; NA = not assessed; T1/2 = elimination half-life; T<sub>max</sub> = time to maximum plasma concentration.

<sup>a</sup> CTD: Module 2.7.1; Table 2.7.1.4, page 15.

<sup>b</sup> 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.<sup>viii</sup>

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  $\geq 1\%$  in absolute anti-insulin antibody levels and a relative increase of  $\geq 30\%$  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."<sup>5</sup> 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<sup>6</sup>**

| Study Alias            | Objective                                                                                                                                                             | Study Population                  | Number of Subjects Randomized                                                          |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------|
| <b>Phase 1 Studies</b> |                                                                                                                                                                       |                                   |                                                                                        |
| ABEO                   | Comparison of the PK and PD of LY2963016 and US-approved LANTUS <sup>®</sup>                                                                                          | Healthy subjects                  | 91                                                                                     |
| ABEA                   | Comparison of the PK and PD of LY2963016 and EU-approved LANTUS <sup>®</sup>                                                                                          | Healthy subjects                  | 80                                                                                     |
| ABEN <sup>a</sup>      | Comparison of the PK and PD of EU- and US-approved LANTUS <sup>®</sup>                                                                                                | Healthy subjects                  | 40                                                                                     |
| ABEI                   | Relative bioavailability of LY2963016 to EU-approved LANTUS <sup>®</sup>                                                                                              | Healthy subjects                  | 16                                                                                     |
| ABEE                   | Comparison of the PD of LY2963016 and EU-approved LANTUS <sup>®</sup>                                                                                                 | Patients with T1DM                | 20                                                                                     |
| ABEM                   | Relative bioavailability of LY2963016 to EU-approved LANTUS <sup>®</sup>                                                                                              | Healthy subjects                  | 24                                                                                     |
| <b>Phase 3 Studies</b> |                                                                                                                                                                       |                                   |                                                                                        |
| ABEB                   | Comparison of LY2963016 with LANTUS <sup>®</sup> (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<br>LANTUS <sup>®</sup> : 267<br>(US-approved: 96/<br>EU-approved: 171)  |
| ABEC                   | Comparison of LY2963016 with LANTUS <sup>®</sup> (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<br>LANTUS <sup>®</sup> : 380<br>(US-approved: 215/<br>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:<sup>5</sup>



- 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<sup>7</sup> — 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.<sup>7</sup> 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.<sup>8</sup>

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.<sup>9</sup>

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<sup>10</sup> — 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<sup>7,10</sup> — 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<sup>2</sup> in the type 1 diabetes mellitus study and 32 kg/m<sup>2</sup> 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.,<sup>4</sup> 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,<sup>ix</sup> 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<sup>x</sup> (approved trade name in Europe; formerly known as Abasria) in pediatric patients older than two years of age based on established similarity to Lantus<sup>xi</sup> 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.<sup>xii</sup>
- 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.<sup>xiii</sup>
- 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.<sup>xiv</sup>

#### 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,<sup>xv</sup> 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."<sup>xvi</sup>

#### **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.”<sup>11</sup>

The Health Canada Reviewer’s Reports noted that the decision to extrapolate an indication is based on several principles:<sup>11</sup>

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.<sup>11</sup>

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.”<sup>11</sup> The European Medicines Agency allowed a slightly wider extrapolation to diabetic children aged two years and older.<sup>12</sup>

## 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/<br>Comparator | Strength        | Dosage<br>Form                                             | Price Per Unit of<br>Insulin (\$)                                                                | Recommended Dose                                                                                                                                                                                                                                                                                              | Average Drug<br>Cost (\$)            |
|---------------------|-----------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Basaglar            | 100<br>units/mL | Solution for<br>injection<br>(cartridge<br>or<br>KwikPen)  | \$0.0526<br><br>(Source: Data on<br>file, Eli Lilly<br>Canada Inc.)                              | Insulin-naïve patients with type 2<br>diabetes: Start at a dose of 10<br>units once daily, and subsequently<br>adjust according to the patient's<br>need<br><br>Switches from Lantus: The dose of<br>Basaglar should be the same as<br>Lantus<br><br>(Source: Basaglar Product<br>Monograph <sup>xvii</sup> ) | Based on<br>50 units/day<br>\$2.6307 |
| Lantus              | 100<br>units/mL | Solution for<br>injection<br>(cartridge<br>or<br>SoloSTAR) | \$0.0619<br><br>(Source:<br>IMS-Brogan Delta<br>PA: Ontario<br>Wholesale<br>[September<br>2015]) | Insulin-naïve patients with type 2<br>diabetes: Start at a dose of 10 U<br>once daily, and subsequently<br>adjust according to the patient's<br>need<br><br>(Source: Lantus Product<br>Monograph <sup>xviii</sup> )                                                                                           | Based on<br>50 units/day<br>\$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 |
|------------------------------------------|-----------------|-------------------------------------------------------------|-------------------------|----------------------------|---------------------------------------------------------------|-----------------------------------------------------|
| <b>Long-acting insulin analogues</b>     |                 |                                                             |                         |                            |                                                               |                                                     |
| <b>Insulin glargine (Basaglar)</b>       | <b>100 U/mL</b> | <b>5 × 3 mL cartridge<br/>5 × 3 mL disposable pen</b>       | <b>78.90<br/>78.90</b>  | <b>0.0526<br/>0.0526</b>   | <b>Reference</b>                                              |                                                     |
| Insulin glargine (Lantus)                | 100 U/mL        | 5 × 3 mL cartridge<br>5 × 3 mL disposable pen<br>10 mL vial | 92.85<br>92.85<br>61.69 | 0.0619<br>0.0619<br>0.0617 | 0.0093<br>0.0093<br>0.0091                                    | 17.7<br>17.7<br>17.3                                |
| Insulin detemir (Levemir)                | 100 U/mL        | 5 × 3 mL cartridge<br>5 × 3 mL disposable pen               | 106.76<br>107.29        | 0.0712<br>0.0715           | 0.0186<br>0.0189                                              | 35.4<br>35.9                                        |
| <b>Intermediate-acting human insulin</b> |                 |                                                             |                         |                            |                                                               |                                                     |
| Insulin isophane (Humulin NPH)           | 100 U/mL        | 5 × 3 mL cartridge<br>10 mL vial                            | 45.12<br>22.99          | 0.0301<br>0.0230           | −0.0225<br>−0.0296                                            | −42.8<br>−56.3                                      |
| Insulin isophane (Novolin ge NPH)        | 100 U/mL        | 5 × 3 mL cartridge<br>10 mL vial                            | 44.34<br>22.56          | 0.0296<br>0.0226           | −0.0230<br>−0.0300                                            | −43.7<br>−57.0                                      |

vs. = versus.

Source: Ontario Drug Benefit prices (accessed January 2016).<sup>13</sup>

### 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.”<sup>5</sup>

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<sup>xix</sup>**



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

**FIGURE 2: SIX-MONTH ACCELERATED REVERSED-PHASE PURITY CHROMATOGRAMS<sup>xx</sup>**



*\*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<sup>xxi</sup>**

*\*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)<sup>xxii</sup>**

*\*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<sup>xxiii</sup>**

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

## CDR SUBSEQUENT ENTRY BIOLOGIC REVIEW REPORT FOR BASAGLAR

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

AUC = area under the curve; CI = confidence interval; C<sub>max</sub> = maximum plasma concentration; CV = coefficient of variation; EU = European Union; EU IGlár = EU-approved Lantus; G<sub>tot</sub> = total glucose infusion over the clamp duration; LS = least squares; LY IGlár = Basaglar; n = number of observations; N = number of patients; R<sub>max</sub> = maximum glucose infusion rate; T<sub>max</sub> = time to maximum plasma concentration; US = United States; US IGlár = US-approved Lantus.

<sup>a</sup> Summary statistics of pharmacokinetic and pharmacodynamic parameters; does not reflect results of the statistical analysis.

<sup>b</sup> The test treatment in each comparison.

<sup>c</sup> Statistical model: log(parameter) = period + sequence + treatment + error, subject (random), period sequence treatment (categorical).

<sup>d</sup> Median or median difference (95% CI) are presented for T<sub>max</sub>. T<sub>max</sub> was analyzed using a nonparametric approach based on the Hodges-Lehmann method. Analysis was based on patient's T<sub>max</sub> 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 <sup>a</sup> | NT <sup>b</sup> | 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.

<sup>a</sup> 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.

<sup>b</sup> 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-5bafa4cf9d9c/pt-formulary-listing-aug-26-2015.pdf.aspx](http://www.diabetes.ca/getmedia/c614895c-d849-44c4-bd4a-5bafa4cf9d9c/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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>BC</b> | <p><b>Type 1 Diabetes — Patient of Any Age</b><br/> 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:</p> <ol style="list-style-type: none"> <li>Has experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management OR</li> <li>Has experienced or continues to experience severe, systemic, or local allergic reaction to existing insulin treatment</li> </ol> <p><b>Type 2 Diabetes — Patient older than 17 years of age only</b><br/> 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:</p> <ol style="list-style-type: none"> <li>Has experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management OR</li> <li>Has experienced or continues to experience severe, systemic or local allergic reaction to existing insulin treatment</li> </ol> <p><b>Practitioner Exemptions</b><br/> Practitioners in the following specialty are not required to submit a Special Authority Request form for coverage: Endocrinology.</p> <p><b>Special Notes</b></p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul> |
| <b>MB</b> | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>NB</b> | For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND: <ul style="list-style-type: none"> <li>have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND</li> <li>have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management</li> <li>OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>NS</b> | For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND: <ul style="list-style-type: none"> <li>have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND</li> <li>have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management</li> <li>OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>PE</b> | For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND: <ul style="list-style-type: none"> <li>have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND</li> <li>have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management</li> <li>OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

**CDR SUBSEQUENT ENTRY BIOLOGIC REVIEW REPORT FOR BASAGLAR**

| Drug Plan | Criteria for Restricted Benefit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>NL</b> | <p>For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin AND:</p> <ul style="list-style-type: none"><li>• have previously taken insulin NPH and/or pre-mix daily at optimal dosing AND</li><li>• have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management</li><li>• OR have documented severe or continuing systemic or local allergic reaction to existing insulin(s).</li></ul>                                                                                          |
| <b>YK</b> | <p>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:</p> <ul style="list-style-type: none"><li>• have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management OR</li><li>• have documented severe or continuing allergic reaction to existing insulin (full documentation required).</li></ul> <p>Must be prescribed by an endocrinologist or visiting internal medicine specialist. Specialists consult to be provided.</p> |

## 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 BIOTEC Canada, 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.")



## REFERENCES

### CDR References

1. Basaglar™ (insulin glargine [rDNA origin]): solution for injection, 100 units/mL [product monograph]. Scarborough (ON): Eli Lilly Canada Inc.; 2015 Sep 1.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 -. Identifier NCT01421147, A study in adults with type 1 diabetes (ELEMENT 1). Outcome measure 7. Secondary: Adult Low Blood Sugar Survey (ALBSS); 2014 Oct 3 [cited 2015 Dec 23]. Available from: <https://clinicaltrials.gov/show/NCT01421147?sect=Xd0156#outcome7>
3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 -. Identifier NCT01421147, A study in adults with type 1 diabetes (ELEMENT 1). Outcome measure 8. Secondary: Insulin Treatment Satisfaction Questionnaire (ITSQ); 2014 Oct 3 [cited 2015 Dec 23]. Available from: <https://clinicaltrials.gov/show/NCT01421147?sect=Xed0156#outcome8>
4. Hadjiyianni I, Dahl D, Lacaya LB, Pollom RK, Chang CL, Ilag LL. The efficacy and safety of LY2963016 insulin glargine in patients with type 1 and type 2 diabetes previously treated with insulin glargine. *Diabetes Obes Metab*. 2016 Jan 7.
5. Health Canada. Summary basis of decision (SBD): Basaglar [Internet]. Ottawa: Health Canada, Health Products and Food Branch; 2015 Nov 2. [cited 2015 Dec 10]. Available from: [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd\\_smd\\_2015\\_basaglar\\_177405-eng.php#sbd](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2015_basaglar_177405-eng.php#sbd)
6. Module 2.5. Clinical overview. LY2963016 type 1 and type 2 diabetes mellitus [**CONFIDENTIAL** manufacturer's submission]. Indianapolis (IN): Eli Lilly and Company; 2014 Jul 16.
7. Blevins TC, Dahl D, Rosenstock J, Ilag LL, Huster WJ, Zielonka JS, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus(R)) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab*. 2015 Aug;17(8):726-33.
8. Center for Drug Evaluation and Research. Guidance for industry. Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention [draft guidance] [Internet]. Silver Spring (MD): Food and Drug Administration; 2008 Feb. [cited 2015 Dec 10]. Available from: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf>
9. Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuse JP. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Inf J* [Internet]. 2008 [cited 2015 Dec 10];42:303-19. Available from: <http://ferran.torres.name/download/shared/missing/DIJ%20Mallinckrodt%20MMRM.pdf>
10. Rosenstock J, Hollander P, Bhargava A, Ilag LL, Pollom RK, Zielonka JS, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus(R)) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes Obes Metab*. 2015 Aug;17(8):734-41.
11. Health Canada reviewer's report: Basaglar (insulin glargine [rDNA origin]) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2015 Aug.
12. European Medicines Agency. EPAR. Assessment report: Abasria (insulin glargine) [Internet]. London: The Agency; 2014 Jun 26. [cited 2015 Dec 10]. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002835/WC500175383.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf)

13. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: The Ministry; 2015. [cited 2016 Jan 7]. Available from: <https://www.healthinfo.moh.gov.on.ca/formulary/>

## Manufacturer References

- <sup>i</sup> Basaglar Product Monograph (Canada). September 2015
- <sup>ii</sup> Basaglar NDS. Common Technical Document. Module 2.3. Comparative Assessment. Page 17.
- <sup>iii</sup> Basaglar NDS. Common Technical Document. Module 2.3. Comparative Assessment. Page 18-19.
- <sup>iv</sup> Linnebjerg H, Lam, E, Seger M, et al. Comparison of the pharmacokinetics and Pharmacodynamics of LY2963016 Insulin Glargine and European Union- and U.S. –Approved Versions of Lantus Insulin Glargine in Healthy Subjects: Three Randomized Euglycemic Clamp Studies. *Diabetes Care*. 2015; Published online August 25, 2015
- <sup>v</sup> Blevins TC, Dahl D, Rosenstock J. Efficacy and Safety of LY2063016 compared with insulin glargine (Lantus<sup>®</sup>) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT1 Study. *Diabetes, Obesity and Metabolism*. 2015;17:726-33.
- <sup>vi</sup> Rosenstock J, Hollander P, Bhargava A. Similar Efficacy and Safety of LY3963016 insulin glargine and insulin glargine (Lantus<sup>®</sup>) in patients with type 2 diabetes who are insulin-naïve or previously treated with insulin glargine: a randomized, double-blind, controlled trial (the ELEMENT 2 study). *Diabetes, Obesity and Metabolism*. 2015;17:734-41.
- <sup>vii</sup> Clinical Study Report. ABEO. Data on file. Eli Lilly and Company
- <sup>viii</sup> Ibid. Basaglar Product Monograph (Canada). September 2015
- <sup>ix</sup> Ibid. Basaglar Product Monograph (Canada). September 2015.
- <sup>x</sup> Abasaglar (formerly Abasria) Product Monograph (EMA). June 2014. Accessed online at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002835/human\\_med\\_001790.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002835/human_med_001790.jsp&mid=WC0b01ac058001d124)
- <sup>xi</sup> European Medicines Agency. Assessment Report for Abasria. June 2014. Page (65 of 65) Accessed online at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002835/WC500175383.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf)
- <sup>xii</sup> Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K. Comparative Trial Between Insulin Glargine and NPH Insulin in Children and Adolescents With Type 1 Diabetes. *J Pediatr Endocrinol Metab.*, 15 (2002), pp. 369–376
- <sup>xiii</sup> Murphy NE Keane SM, Ong KK, et al. A randomized cross-over trial comparing insulin glargine plus lispro with NPH insulin plus soluble insulin in adolescents with type 1 diabetes. *Diabetes*. 2002;51(Suppl 2):A54. Abstract.
- <sup>xiv</sup> Dunger DB, Edge JA, Skvor J. Insulin glargine provides long-term effective glycemic control in children and adolescents with type 1 diabetes. *Diabetes*. 2002;51(Suppl 2): A426. Abstract.
- <sup>xv</sup> Basaglar (formerly Abasria) Product Monograph (Australia). November 2014. Accessed online at: <http://www.tga.gov.au/auspar/auspar-insulin-glargine>
- <sup>xvi</sup> Australian Public Assessment Report for Insulin Glargine. August 2015 (page 46 of 48). Accessed online at: <http://www.tga.gov.au/auspar/auspar-insulin-glargine>
- <sup>xvii</sup> Ibid. Basaglar Product Monograph (Canada). September 2015.
- <sup>xviii</sup> Ibid. Lantus Product Monograph (Canada). July 2015.
- <sup>xix</sup> Basaglar NDS. Common Technical Document. Module 2.3. Comparative Assessment. Page 18
- <sup>xx</sup> Basaglar NDS. Common Technical Document. Module 2.3. Comparative Assessment. Page 19
- <sup>xxi</sup> Basaglar NDS. Common Technical Document. Module 2.3. Comparative Assessment. Page 25
- <sup>xxii</sup> Basaglar NDS. Common Technical Document. Module 2.7.4. Clinical Safety Summary. Page 28.
- <sup>xxiii</sup> Ibid. Linnebjerg et al.